THE UNIVERSITY OF ALBERTA

SYNTHESES AND SPECTRAL STUDIES OF SOME NEW MANNICH BASES

by

KRISHAN KUMAR KHULLAR

A THESIS

Submitted to the Faculty of Graduate Studies in
partial fulfilment of the requirements for the
degree of Master of Science.

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled:

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"In the absence of any considerable numbers of trustworthy generalisations that relate chemical structure and physiological activity, the only means of learning of the effects of such relationships are to prepare compounds of slight structural differences and study the effects of such changes."

ABSTRACT

The use of 2,6-dimethylmorpholine as an amine moiety in the Mannich reaction has been investigated. Thirteen new bases have been synthesized using different ketones. The use of 2,6-dimethylmorpholine in the Mannich reaction has been extended by allowing it to react with two different phenolic compounds. The product obtained from α-naphthol was found to have no nitrogen. Probable structures have been assigned to this compound and the mechanisms of their formation discussed. The β-amino acids have also been synthesized by Mannich reaction. The resulting acids have been esterified by thionyl chloride and methanol to yield the corresponding β-amino ester salts. All attempts to use 2,6-dimethylpiperidine, 2-methylpiperidine and p-chlorophenylacetic acid in the Mannich reaction have been unsuccessful. However, 3-methylpiperidine has been successfully used in the Mannich reaction. The structures of the compounds have been established by infrared spectroscopy, mass spectrometry and elemental analysis. An attempt has also been made to correlate mass spectral data with antispasmodic activity of certain Mannich bases.

ACKNOWLEDGEMENTS

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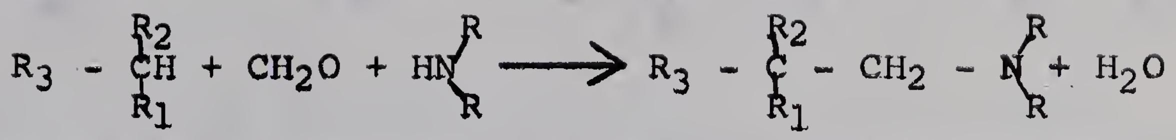
INTRODUCTION

INTRODUCTION

The providing of medicinal agents and the eradication of disease has been one of our most complex social problems since the beginning of man-kind. The service of chemistry to medicine represents one of the most fascinating facets of the story of application of scientific knowledge to the welfare of humanity. Stemming from the use of medicinal plants by herbalists as far back in history as the time of ancient Greece; the utilization of the plant kingdom and of the active principles isolated from plants has developed in recent years into a systematic search for new drugs and their synthesis in the laboratories. Interest in recent years has developed to the extent of preparing purely synthetic compounds and to establishing a structure-activity correlation. In view of the need to duplicate in laboratory the preparation of natural products as well as to synthesize new medicinal agents, the Mannich reaction (1) would appear to fill an important role. In addition, this reaction has acquired enhanced interest with the growing realization that it may well be the characteristic step in alkaloid biogenesis (2).

The Mannich reaction consists of the condensation of either ammonia or a primary or a secondary amine usually as the hydrochloride with formaldehyde and a compound containing at least one hydrogen atom of pronounced activity. In general form, the reaction may be represented as follows:

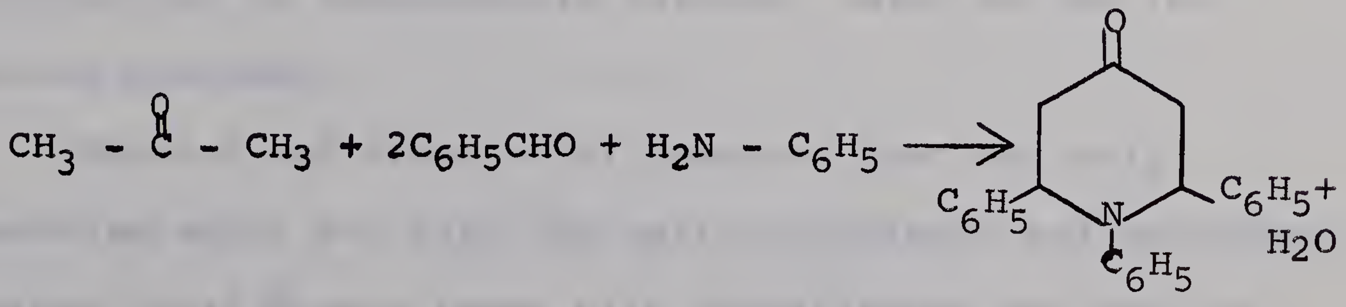


$$R_3 - \underset{R_1}{\overset{R_2}{\mathrm{CH}}} + \mathrm{CH_2O} + \mathrm{HN}\begin{smallmatrix}R\\R\end{smallmatrix} \longrightarrow R_3 - \underset{R_1}{\overset{R_2}{\mathrm{C}}} - \mathrm{CH_2} - \mathrm{N}\begin{smallmatrix}R\\R\end{smallmatrix} + \mathrm{H_2O}$$

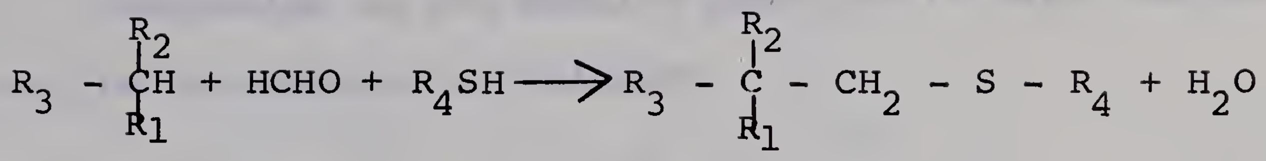
The active hydrogen compound most frequently contains ketone, an acid, an ester or a keto ester as a functional group, although phenols, aldehydes, indoles, thiophenes furans, nitroalkanes (3) etc. have been used as well.

Aldehydes other than formaldehyde may be used in certain condensations of the Mannich type. Those which have been studied are acetaldehyde, benzaldehyde and anisaldehyde, but the reactions involving these appear to be limited to ammonia and primary amines and their salts. (1)

Frequently, products derived from two moles of benzaldehyde and one mole of primary amine are unstable and readily undergo cyclization, (1)



The Mannich reaction may be carried out with equal ease by substituting thiol for the amine. (4)



$$R_3 - \underset{R_1}{\overset{R_2}{\overset{|}{\underset{|}{C}}}}H + HCHO + R_4SH \longrightarrow R_3 - \underset{R_1}{\overset{R_2}{\overset{|}{\underset{|}{C}}}} - CH_2 - S - R_4 + H_2O$$

where $R_1R_2R_3CH$ represents a compound containing active methylene or methylidyne group.

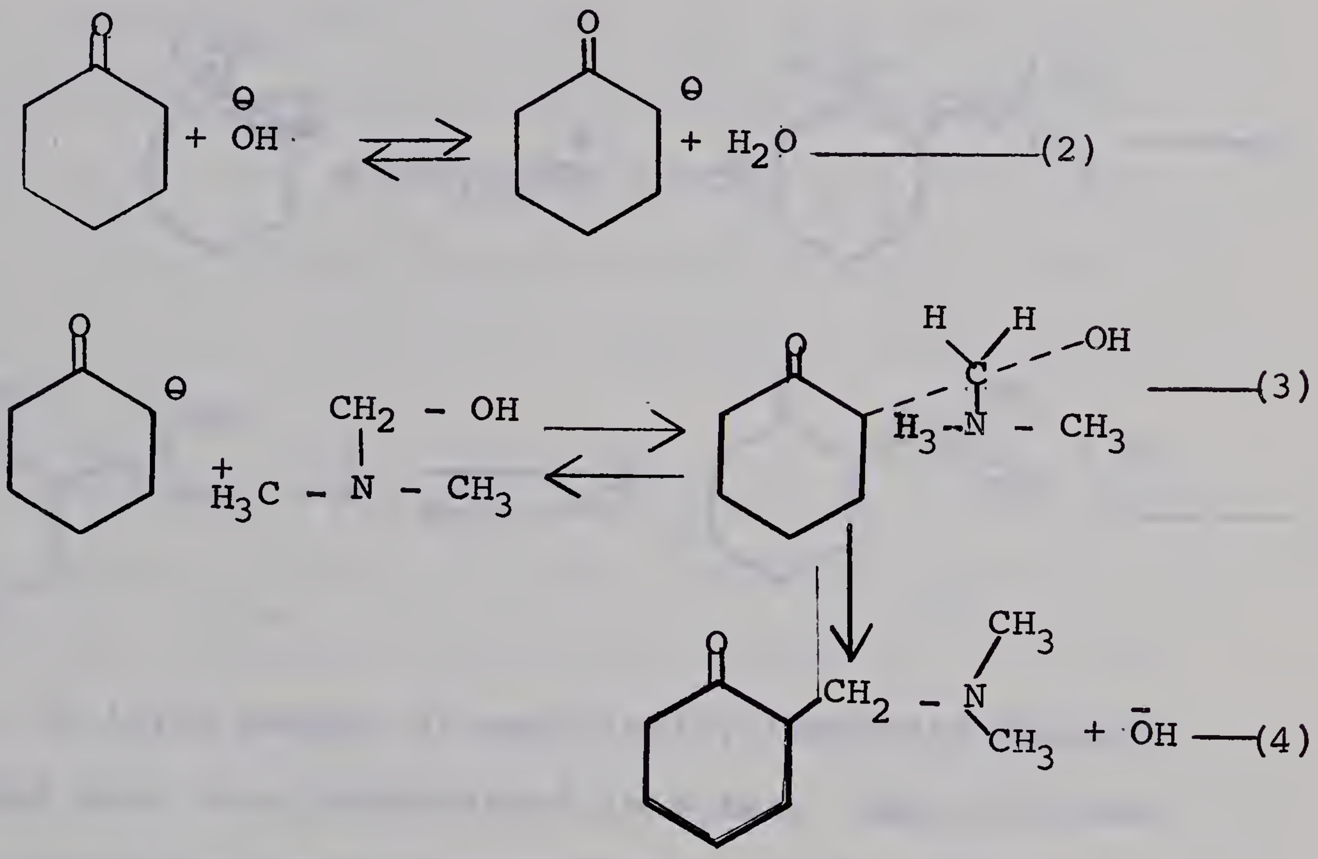
The Mannich reaction has been effected in aqueous media, methanol, ethanol, isoamyl alcohol or an excess of one of the reactants. The use of nitrobenzene and benzene as solvents has also proved effective, giving satisfactory yields in a relatively short reaction time. (5)

The first observation of a condensation of the type known as the Mannich reaction was made by Tollens (6) in 1906 who isolated the tertiary amine $(Ph - \overset{O}{\overset{\|}{C}} - CH_2 - CH_2)_3\ NHCl$ from ammonium chloride, formaldehyde and acetophenone. The detailed study by Mannich begun in 1912 (7) was initiated while investigating the pharmacological effect of mixing several drugs. He observed that formaldehyde, anti-pyrine and ammonium chloride constituted an incompatible mixture, owing to the reaction produced.

Mannich and Krösche (8) observed that not only ammonium salts but also the salts of primary and secondary amines yield β-keto bases with formaldehyde and ketones. Mannich and Braun (9) noted that this type of reaction was not limited to aromatic ketones but could proceed with cyclic ketones and the aliphatic ketones.

Mechanism of the Mannich reaction in basic medium may be represented as follows:

$$(CH_3)_2NH + HCHO \rightleftarrows (CH_3)_2N\ CH_2OH \quad \text{———(1)}$$

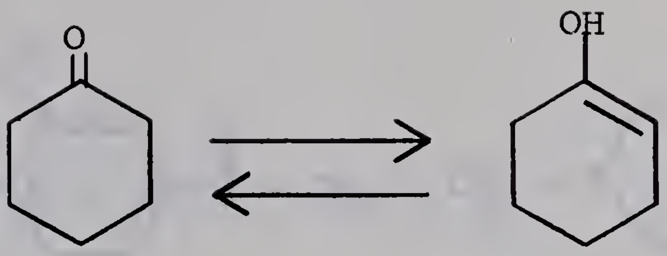


Mechanism of the Mannich reaction in acid medium may be represented by the following equations (10):-

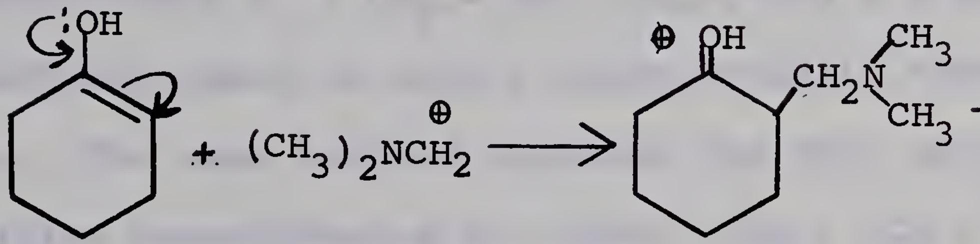
$$(CH_3)_2\overset{\oplus}{N}H_2 + \overset{\ominus}{A} \leftrightarrows (CH_3)_2NH + HA \quad \text{———(5)}$$

$$(CH_3)_2NH + HCHO \rightleftarrows (CH_3)_2\ NCH_2OH \quad \text{———(6)}$$

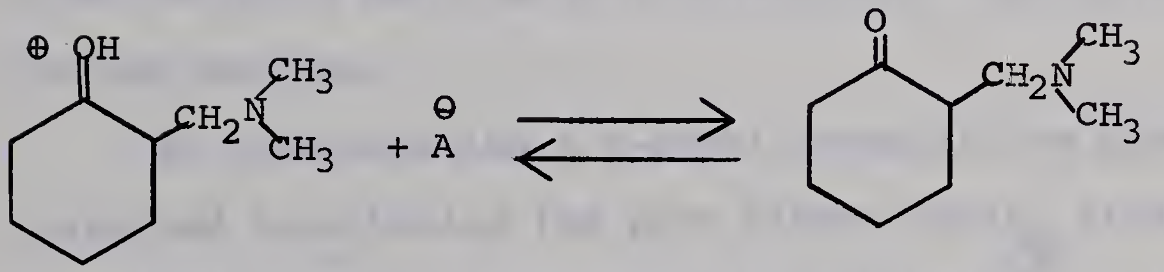
$$(CH_3)_2NCH_2OH + HA \rightleftarrows (CH_3)_2\overset{\oplus}{N}CH_2 + \overset{\ominus}{A} + H_2O \quad \text{———(7)}$$



(8)

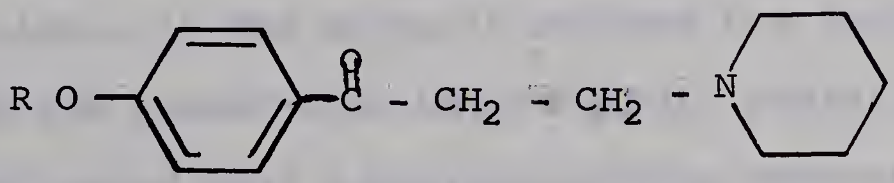


(9)



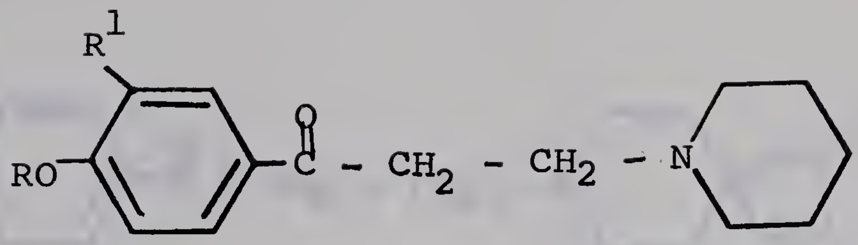
(10)

A large number of medicinally important Mannich bases have been synthesized thus far. Many of these compounds and their intermediates could not be easily prepared by other methods. Two of the amino ketones, 1. Falicaine® (R = Propyl) and Dyclonine (R = Butyl).



have gained considerable recognition as local anaesthetics (11).

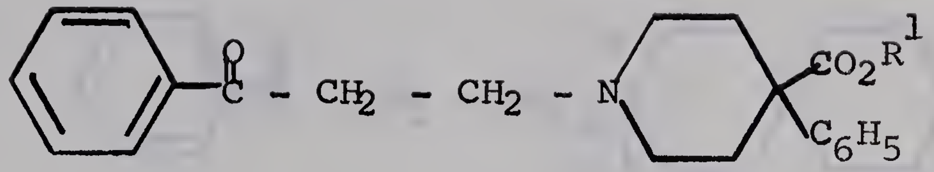
Beani and co-workers (12) reported compounds of the propiophenone type:-



One compound where $R^1 = CH_2 = CH - CH_2-$, and R = Me called AMPP was found to have a lower toxicity than Falicaine. The same authors replaced the keto group in piperidino propiophenone by -CHOH, $-CH_2-$, -CH = CH- and concluded that optimal anaesthetic effect resided in the ketones.

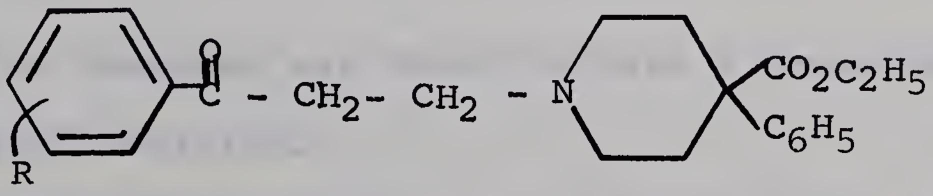
By incorporating a 4-ethyl group in the piperidino ring and lengthening the para alkoxy chain, Profft (13) obtained compounds approximating Falicaine® in their anaesthetic activity by having a substantially longer duration. Replacement of the benzene nucleus of Falicaine by thiophene produced a substantial decrease in the topical effect (14). A few thio analogues of morpholino propiophenones have also been synthesized. The introduction of sulphur in the molecule reduced the toxicity and increased the anaesthetic effect (15). Profft and Zschummel (16) noted that 4-butylpiperidino derivatives of para alkoxypropiophenones were more active than Falicaine. The low water solubility of these compounds, however, prevented their use in medicine.

Janssen et al (17) synthesized Mannich bases of the type:-



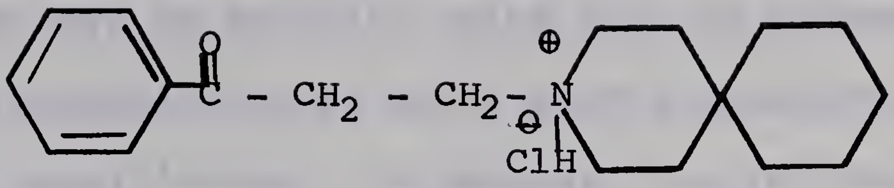
and compared the pharmacological activities of the Mannich bases with variation in the ester group. They concluded, from the results, that shortening, lengthening, introduction of unsaturation or aryl substitution of ethyl group in the ester function resulted in a decrease of the analgesic and mydriatic potency in mice.

Janssen et al (18) prepared additional derivatives of the type:-



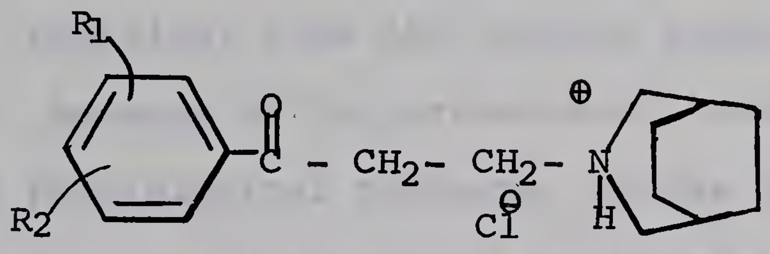
and studied the effect of variation of groups and their position on the benzene ring on the analgesic activity of these compounds. In general, the meta isomer was, on the average, four times more active than the corresponding para isomer. The introduction of more than one substituent in the benzene nucleus resulted in considerable loss of activity.

Handley et al (19) synthesized a Mannich base from 3-azaspiro [5.5] undecane hydrochloride.



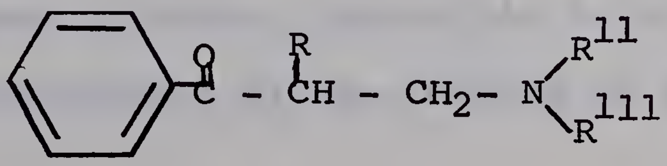
This Mannich base was found to be active against certain larvae.

Blanton and Nobles (20) prepared Mannich bases using 3-azabicyclo[3.2.2]nonane as an amine moiety.



This type of compound was found to have a broad spectrum of antimicrobial activity.

Antispasmodics belonging to a type of basic esters of carboxylic acids suffer from the inherent instability of the ester group to hydrolytic conditions. This prompted Denton and co-workers (21) to synthesize a number of antispasmodics which possessed no ester group. Since certain β-aminoalkyl aryl ketones had been reported to possess this type of activity, they undertook the synthesis and study of the basic ketones having the general formula:-



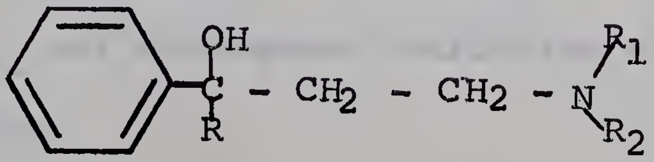
These compounds were prepared through the Mannich reaction. Some of the compounds of this type synthesized by them were found to have an activity twice that of papaverine. The use of piperidine as an amine moiety appeared to be of special significance. In general, the introduction of substituents into the benzene ring of this type of compound was found to decrease the antispasmodic activity, in most instances.

The pyrrole or modified pyrrole nucleus is found in a number of naturally occurring compounds, haemoglobin, chlorophyll, proteins, bile and urinary pigments and certain alkaloids. Because of the presence of this nucleus in so many normal physiological products, Blicke and Blake (22) decided to introduce it into certain synthetic drugs and in order to achieve this objective, they employed 2-acetylpyrrole in the Mannich reaction. The Mannich bases so obtained were found to possess anaesthetic action. Levy and Nisbet (23), however, extended the scope of the Mannich reaction to the preparation of amino ketones derived from 2-acetylthiophene, 2-acetyl- 4-phenyl thiazole, and 2-acetylfuran. These types of Mannich bases showed a local anaesthetic action, which was considerably less than that of cocaine.

In addition to the medicinal uses of βamino ketones, they serve as very important intermediates for the synthesis of various types of compounds which otherwise would be difficult and in some instances impossible to procure. The β-substituted aminoketones may be reduced to the corresponding

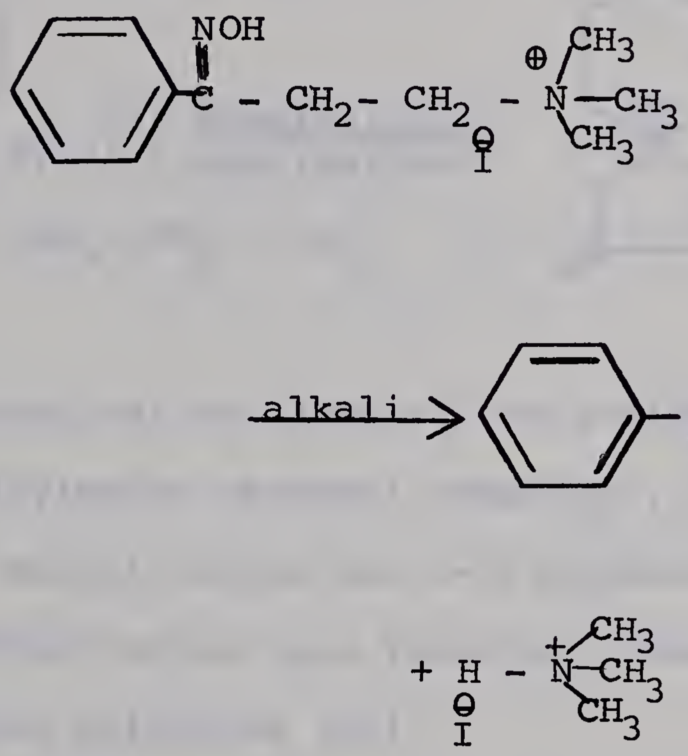
aminoalkanols by various well known methods. (24, 25, 26) These aminoalkanols are more stable than the corresponding ketones. The reduction of aminoketones to corresponding alcohols makes possible the synthesis of compounds which are structurally similar to adrenaline, tyramine, hordenine, etc. but which contain nitrogen in the γ-position. This type of compound caused a fall in blood pressure (25). In addition, some of these analogues have been utilized as antimalarials, (27) analgesics (28) and central nervous system stimulants (29). The aminoalcohols, in the form of their benzoates and para aminobenzoates, find application as local anaesthetics (30).

In view of the fact that structural modifications had such a marked effect on the activity of β-aminoketones, Denton and his co-workers (21) transformed the aminoketones into their corresponding tertiary alcohols of the general formula,

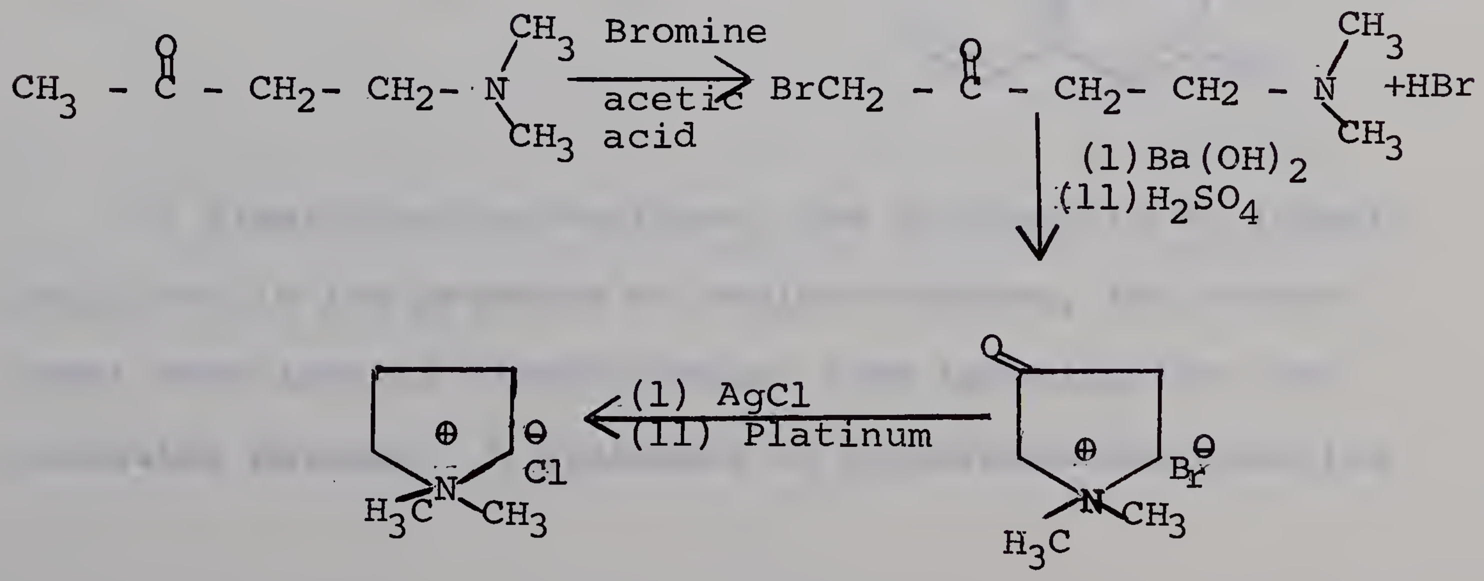


using a Grignard reaction. Almost all the tertiary alcohols thus synthesized showed greater antispasmodic activity than their corresponding aminoketones. The morpholinyl alcohols showed in particular, the greatest increase in activity over that of the parent ketone. It is interesting to note that several of the β piperidino and β pyrrolidino tertiary alcohols find use in the treatment of "Parkinson's" syndrome (31).

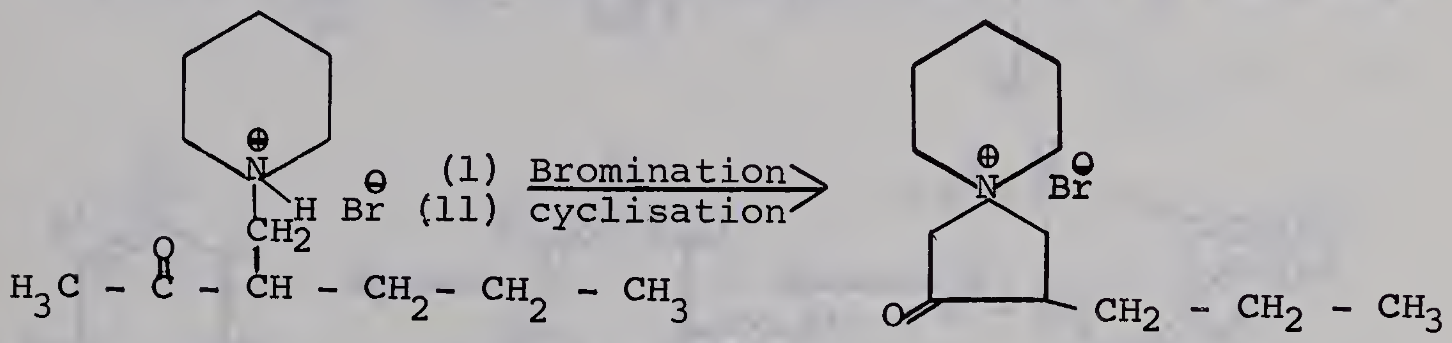
The oximes of Mannich bases are much more stable than the parent ketones, and had often enhanced spasmolytic activity (32). The methiodides of these oximes with alcoholic alkali yielded 3-phenyl-Δ^2-isoxazoline.



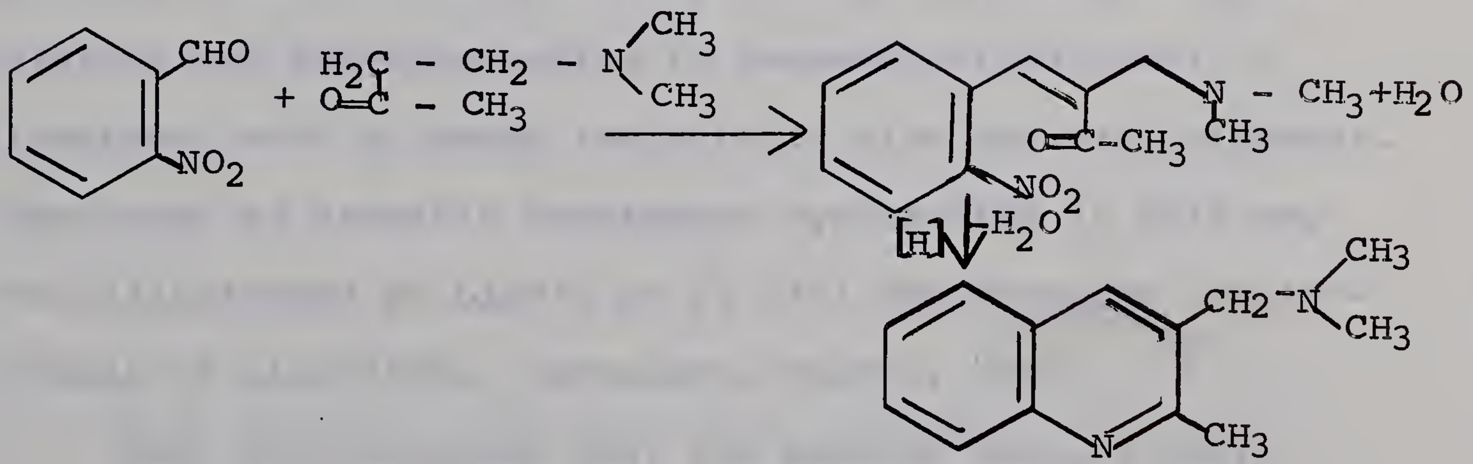
Mannich and Gollasch (33) synthesized N-methyl pyrrolidinium chloride from 1-dimethylamino-3-butanone on bromination, follwed by treatment with Ba(OH)2, sulphuric acid, silver oxide, and subsequent reduction with platinum under pressure.



A very similar method was employed by Mannich and Gollasch (33) to synthesize spiro-1-3-propyl-4-ketopyrrolidinium bromide starting from a corresponding Mannich base.

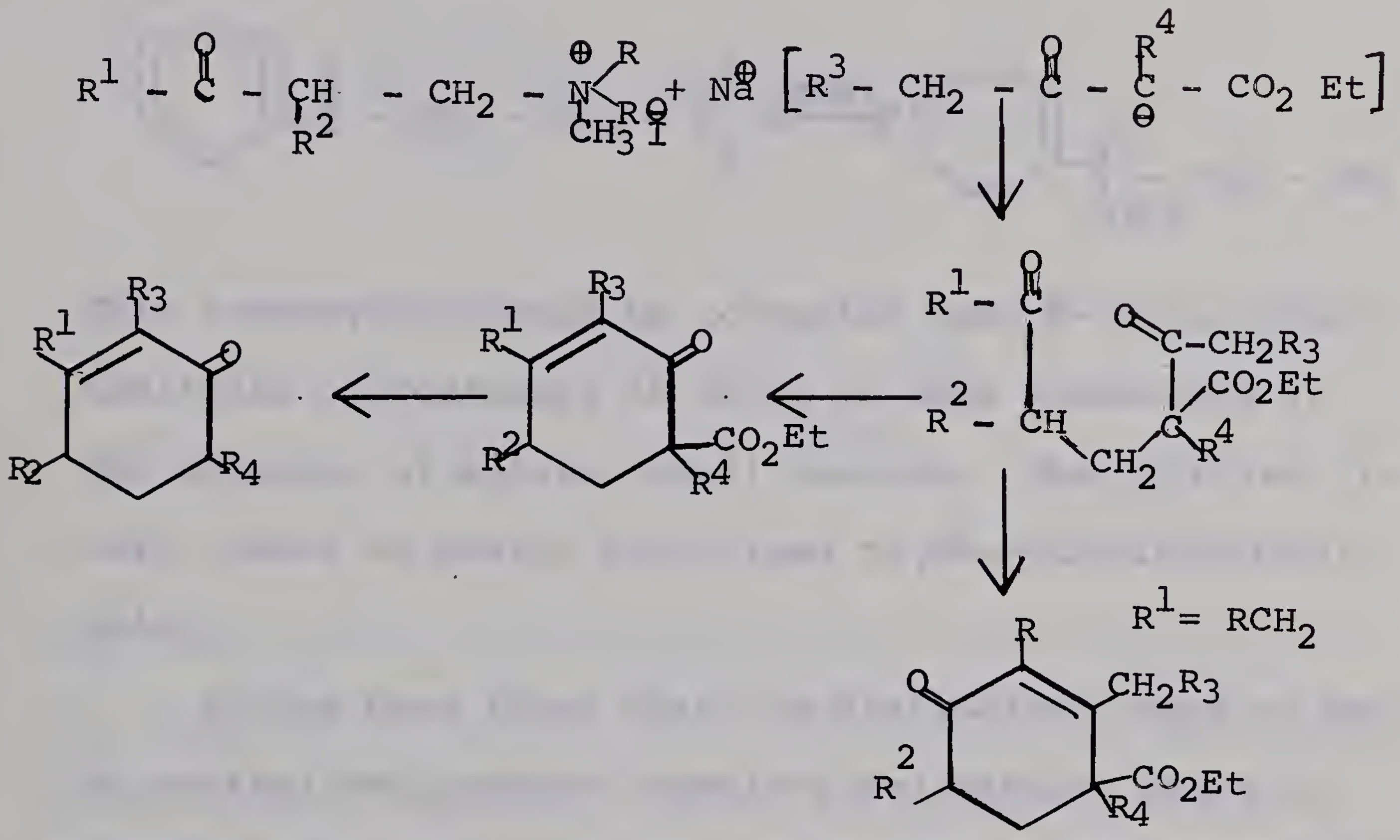


Advantage can be taken of the active methylene group in the dialkylamino carbonyl compounds. Thus β-dimethylaminoethyl methyl ketone and o-nitrobenzaldehyde react to yield a product which upon reduction loses water to form a substituted quinoline (39).



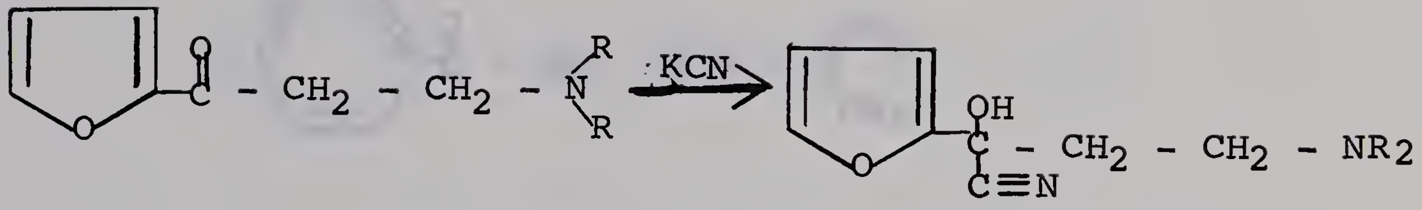
In dimethylamino-3-ketones, the nitrogen is so loosely held that in the presence of sodium ethoxide, the ketones react with loss of dimethylamine, thus behaving like unsaturated ketones. A synthesis of cyclohexenones starting

from the methiodides of the Mannich bases was performed by this method:-



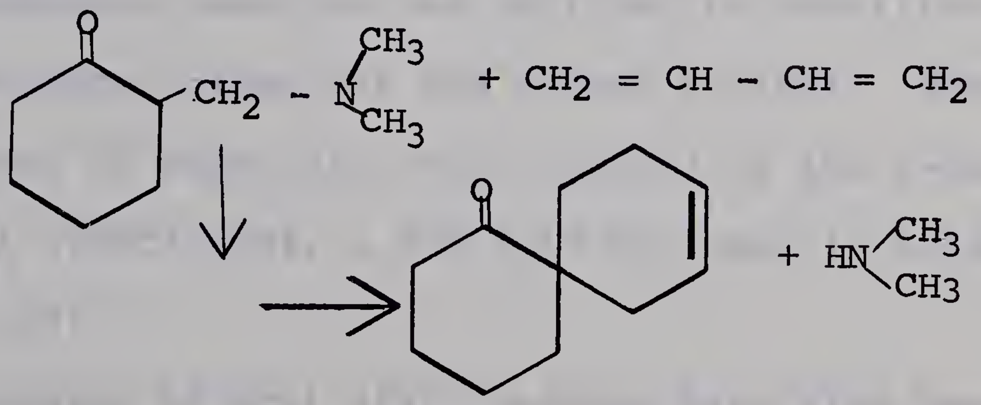
The cyclohexenones may then be converted to aromatic compounds by dehydrogenation to phenols, by reduction, dehydration and dehydrogenation to benzene derivatives; by treatment with Grignard reagents to give tertiary alcohols. The range of aromatic substances synthesized in this way was illustrated by Lion's et al (35) who describe the synthesis of piperitone, carvenone, durene, etc.

Knot (36) reported that the Mannich salt, 2-furyl β- dimethylaminoethyl ketone hydrochloride, on treatment with cold aqueous potassium cyanide, yielded a cyanohydrin of the Mannich base.

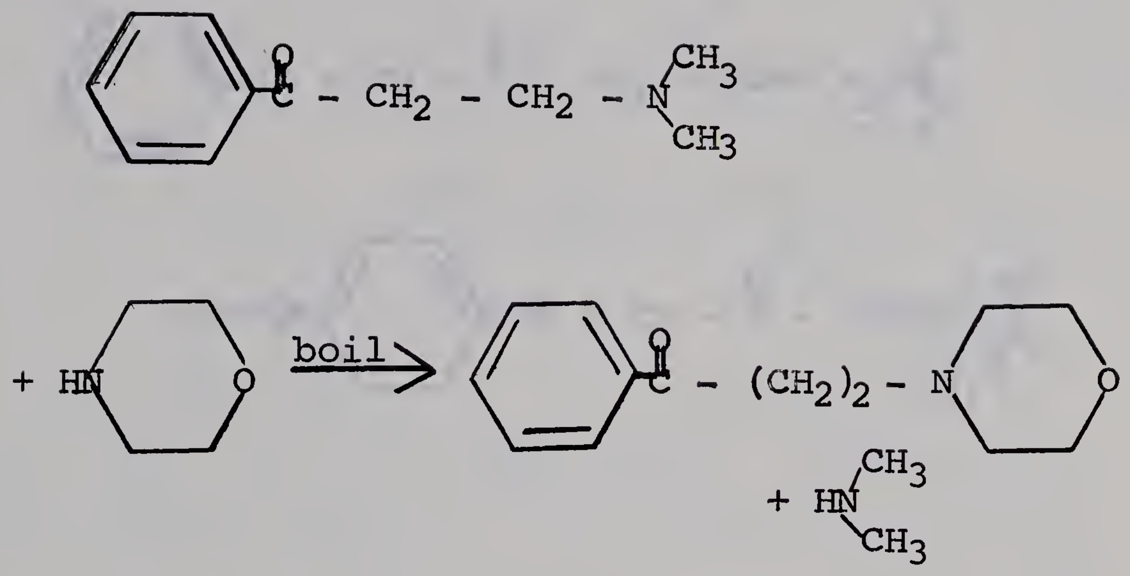


This cyanohydrin could be converted into β-furoyl propionitrile on refluxing in water or more preferably in the presence of excess alkali cyanide. The nitriles, in turn, could be easily hydrolized to β-cycloylpropionic acid.

It has been found that the Diels-Alder reaction may be carried out between butadiene and Mannich bases of α-methylenic cyclic ketones to produce spiro-ketones (37).

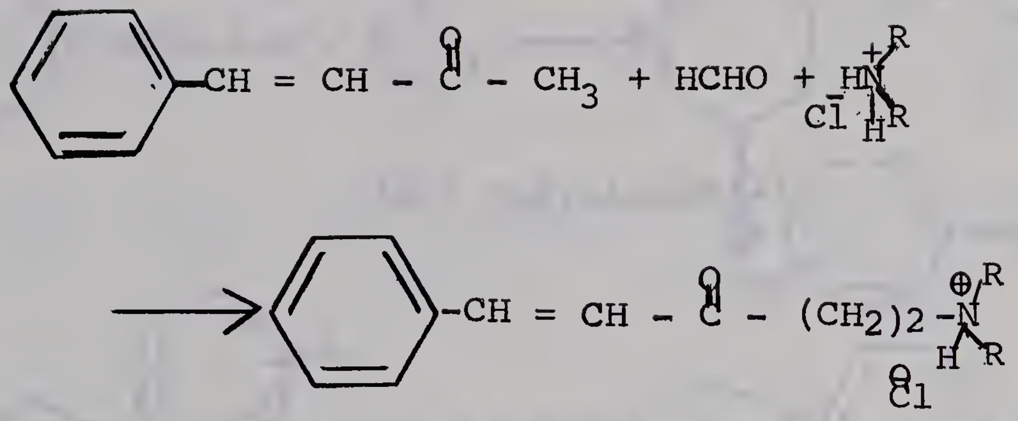


Amine exchange reactions occur when quaternary ammonium salts are heated with ammonia or primary or secondary amines. Snyder and Brewster (38) found that β-dimethyl amino propiophenone reacted with boiling morpholine to give β-morpholinopropiophenone and dimethylamine.



This replacement action appears to be very important for the synthesis of Mannich bases which cannot be obtained by direct Mannich reaction. With nor-morphine, nor-codeine, etc. the direct Mannich reaction failed to proceed, therefore, amine-exchange reaction was utilized to substitute 3-oxo-3-phenylpropyl group for the methyl radical. When the methyl group of meperidine was replaced by the 3-oxo-3-phenylpropyl substituent, a 500 fold increase in potency was observed (39).

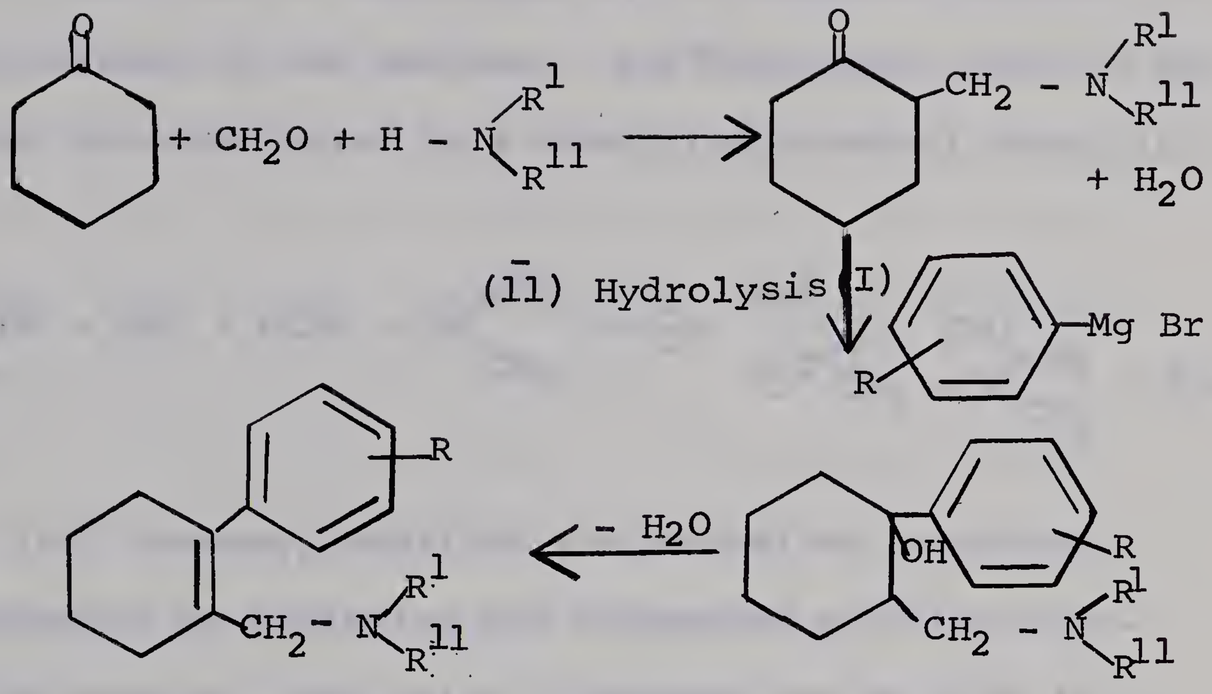
The vinylogues of aryl alkyl ketones have also been employed in the Mannich reaction. Burckhalter and Johnson (40) prepared Mannich bases from benzalacetone as vinylogues of β-amino propiophenones in an attempt to enhance the analgetic effects of the latter.



These bases while devoid of analgetic activity possessed antibacterial action in vitro. The double bond and the carbonyl group in these types of Mannich bases can be selectively reduced with palladium and animal charcoal, and by application of activated aluminum, respectively (41).

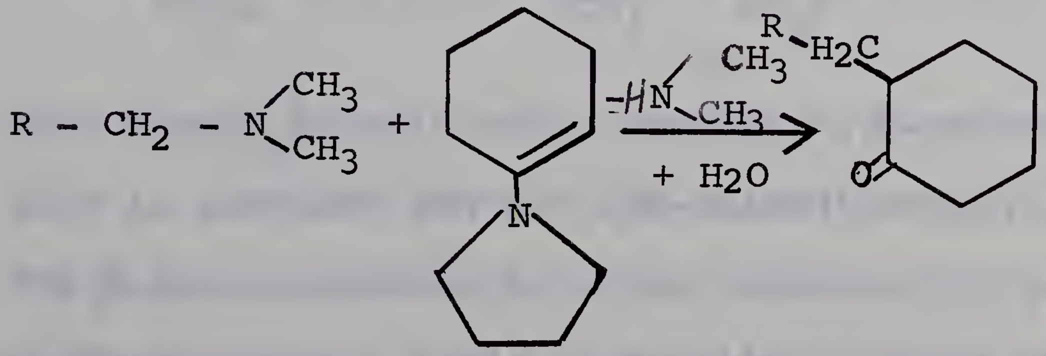
Cyclohexanone reacts readily with piperidine hydrochloride, and formaldehyde to yield 2-piperidinomethyl cyclohexanone hydrochloride. These Mannich bases can be reduced with aluminum amalgam in moist ether to an alcoholic base. The benzoates of these alcohols possess strong local anaesthetic activity (42).

The pharmacological evaluation of morphine-like compounds having relatively simple structures showed that strict adherence to the relationship of the individual atoms in the morphine skeleton is not essential for analgesic activity.

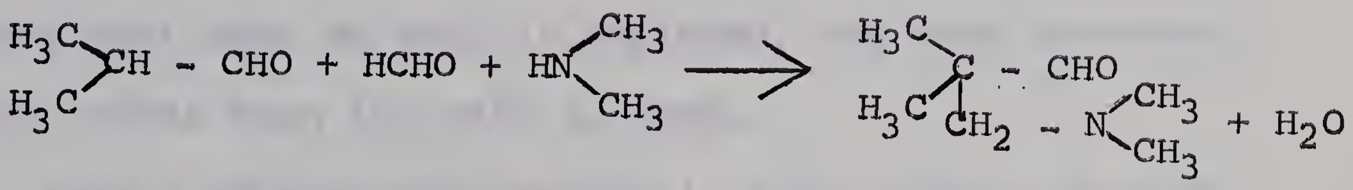


In a type of compound synthesized above, where R was hydroxy or alkyl and R^{1}, R^{11} were alkylene, pronounced analgesic action was observed. The most active compounds were those in which the cyclohexanone residue was replaced by a 1-tetralone residue and nitrogen was part of the piperidino ring (43).

It has been found only recently that the enamine of a ketone is easily alkylated by the Mannich base when equivalent amounts of two substances are heated for twenty-four hours in dioxane or xylene (44).

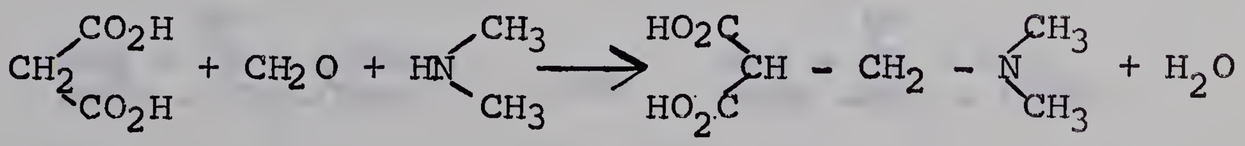


The behaviour of aldehydes in the Mannich reaction is similar to that of the ketones. The α-hydrogen atom of the aldehydes is substituted by a dialkylaminomethyl group (1).



Mannich (45) however, modified the method of preparing aminoaldehydes by replacing the aldehydes with the corresponding acetals. The amino aldehydes can be used for the preparation of the corresponding acids through the oxime and nitrile formation followed by hydrolysis. The benzoates and β-amino benzoates of the alcoholic bases derived from these acids by reduction are of interest as possible anaesthetics (46).

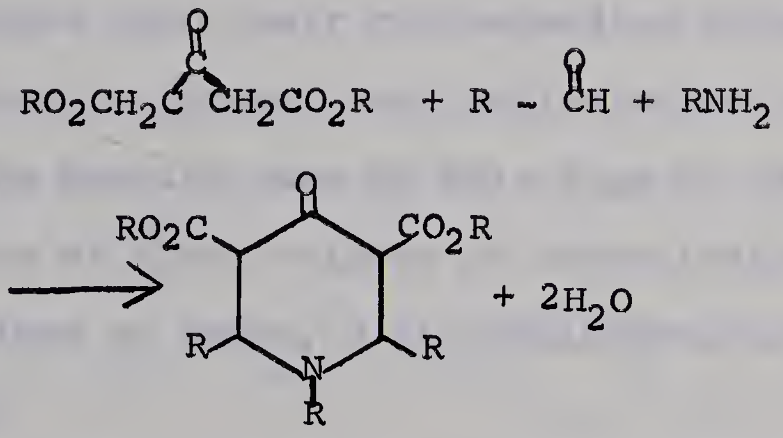
The synthesis of β-aminodicarboxylic acids has been carried out by Mannich reaction with substituted malonic acids having at least one hydrogen on the α-carbon atom.



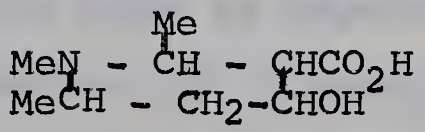
With phenyl malonic acid, however, a β-aminomonocarboxylic acid is produced and not a β-aminodicarboxylic acid (1). The β-aminodicarboxylic acids decompose to give monobasic α,β-unsaturated acids in excellent yields on refluxing in aqueous neutral solution (1). α-Cyanoacetic acid,

paranitrophenylacetic acid, 2, 4-dinitrophenylacetic acid, and ketoacids are also known to undergo Mannich reaction (1). However, conflicting reports appear in literature (1, 47) about the use of ortho-nitromandelic acid. It is noteworthy that when an acid is employed, the free secondary amine rather than its salt is used.

Esters of acetonedicarboxylic acid undergo Mannich reaction with acetaldehyde and either ammonia or primary alkyl or arylalkylamines to produce esters of 2, 6-dimethyl-4-keto piperidine-3, 5-dicarboxylic acid (48).

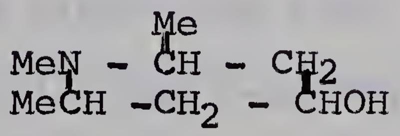


Mannich applied the term 'open' to the molecular structure of the following type:-



$$\begin{array}{l} \text{MeN} - \overset{\text{Me}}{\text{CH}} - \text{CHCO}_2\text{H} \\ \text{MeCH} - \text{CH}_2 - \text{CHOH} \end{array}$$

and

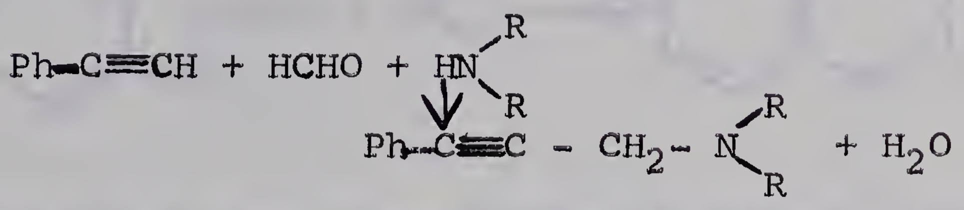


$$\begin{array}{l} \text{MeN} - \overset{\text{Me}}{\text{CH}} - \text{CH}_2 \\ \text{MeCH} - \text{CH}_2 - \text{CHOH} \end{array}$$

and synthesized open ecgonine, cocaine, psicaine, tropinone, tropane, pseudotropine starting with methylamine, acetaldehyde and a suitable keto ester (49). Synthesis of 3-methyl-3-aza-bicyclo (3.3.1)-nonanone as well as derivatives of bispidine were prepared through Mannich reaction utilizing

appropriate keto esters, amines and formalin (50, 51).

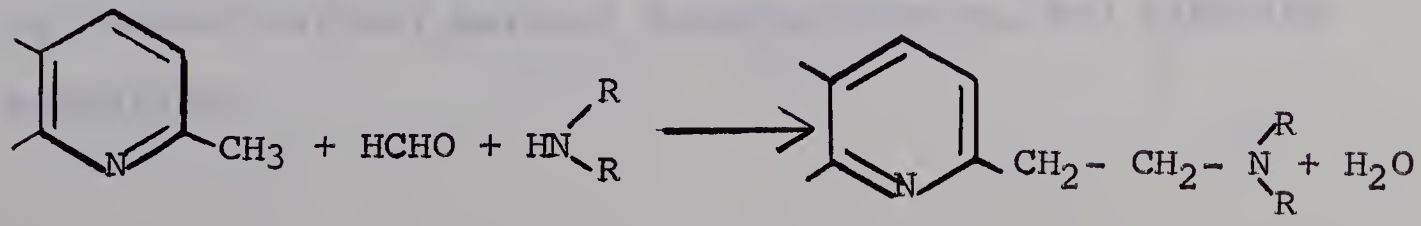
Phenylacetylene and certain substituted phenylacetylenes, such as the 2-nitro, 2-amino and 4-methoxy derivatives react readily with formaldehyde and secondary amines (52) according to the equation:-



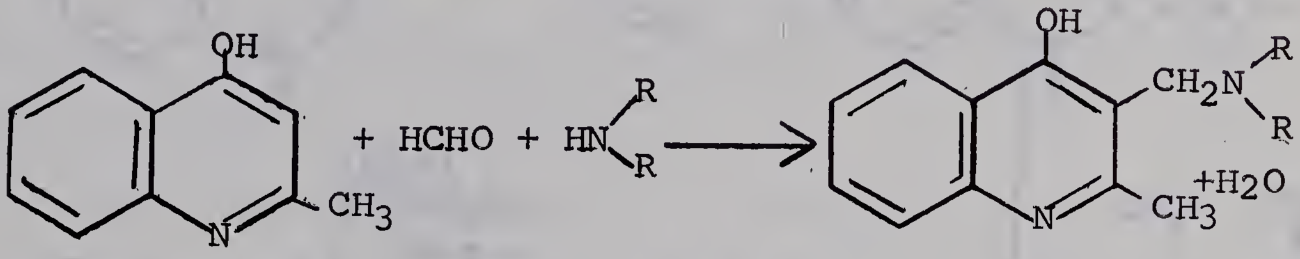
$$Ph-C\equiv CH + HCHO + HN\begin{smallmatrix}R\\ R\end{smallmatrix} \longrightarrow Ph-C\equiv C-CH_2-N\begin{smallmatrix}R\\ R\end{smallmatrix} + H_2O$$

These Mannich bases derived from acetylenic compounds can be transformed into their corresponding propanes on complete hydrogenation in alcohol with palladium and hydrogen. However, if the Mannich base of this type is slowly added to a cold mixture of three volumes of concentrated sulphuric acid and one volume of water, dialkylaminopropiophenone is produced (52).

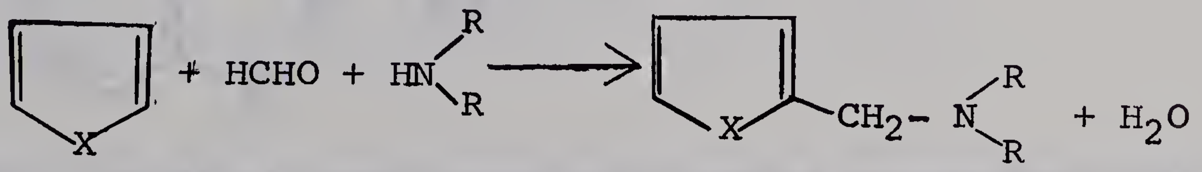
Since the α-methyl groups in a pyridine or quinoline nucleus contain hydrogens of about the same activity as those in the methyl group of a methylketone, the Mannich reaction might be expected to take place with such molecules. α-Picoline (1), 2-methylquinoline (1) and 8-nitroquinoline (1) have been condensed with primary and secondary amines. The subsitution takes place at position 2.



However, Nabih et al (53) observed that for 2-methyl-4-hydroxyquinoline, the dialkylamino substituent was introduced at position 3 instead of at position 2.

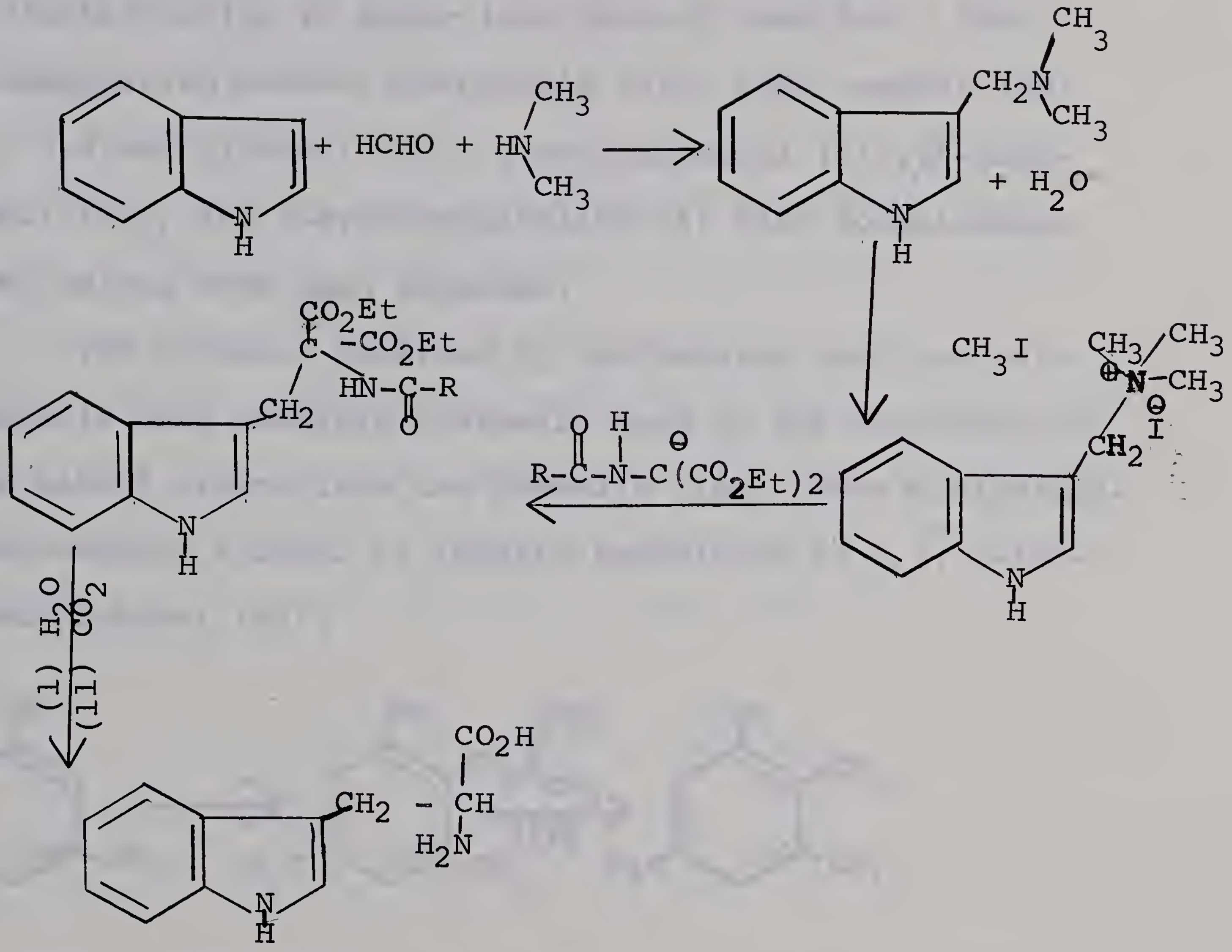


Since the 2- and 5- positions of furans, thiophenes, and pyrroles are known to be active, synthesis of Mannich bases was attempted on pyrrole, (54) and thiophene (55) with no substituent in position 2. A general reaction of the following type was observed in each instance:-



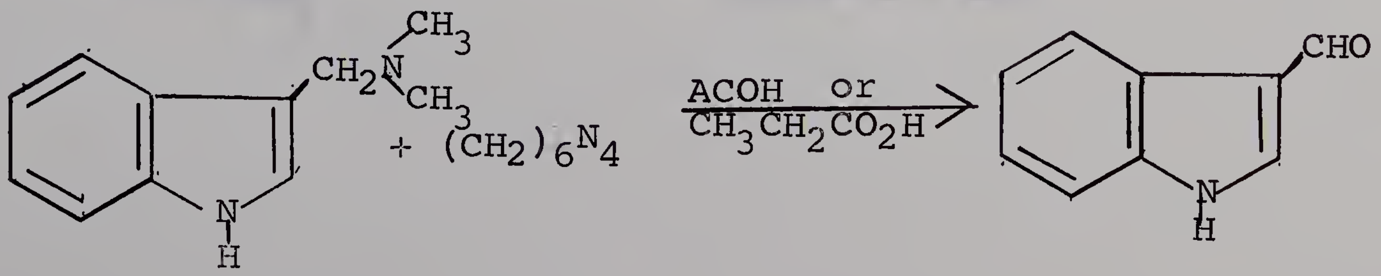
where X may be S. or N.

Gramine (3-dimethylaminomethyl indole) was prepared by Mannich reaction using indole, formaldehyde and dimethylamine. Snyder and Smith (56) synthesized dl-tryptophan by alkylating the sodium derivative of acetaminomalonic ester with Gramine in the presence of dioxane followed by saponification, partial decarboxylation, and alkaline hydrolysis.



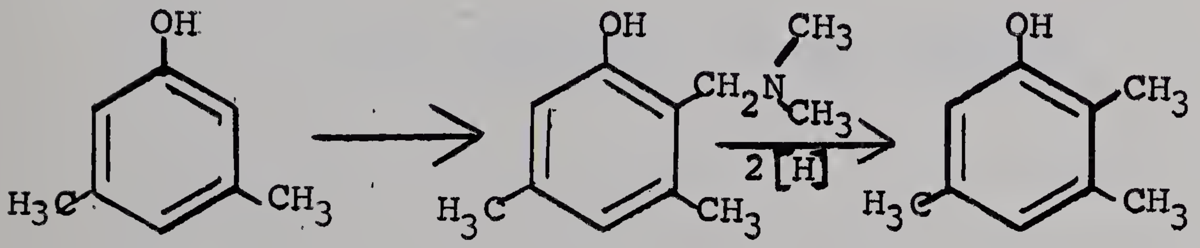
Snyder and Eliel (57) prepared 1-methyl tryptophan using the same procedure as given above excepting that the starting material was 1-methylindole instead of indole.

It is interesting to note that interaction of 3-(dimethylaminomethylindole) with hexamethylenetetramine in acetic acid or dilute propionic acid produces 3-indolecarboxaldehyde (58).

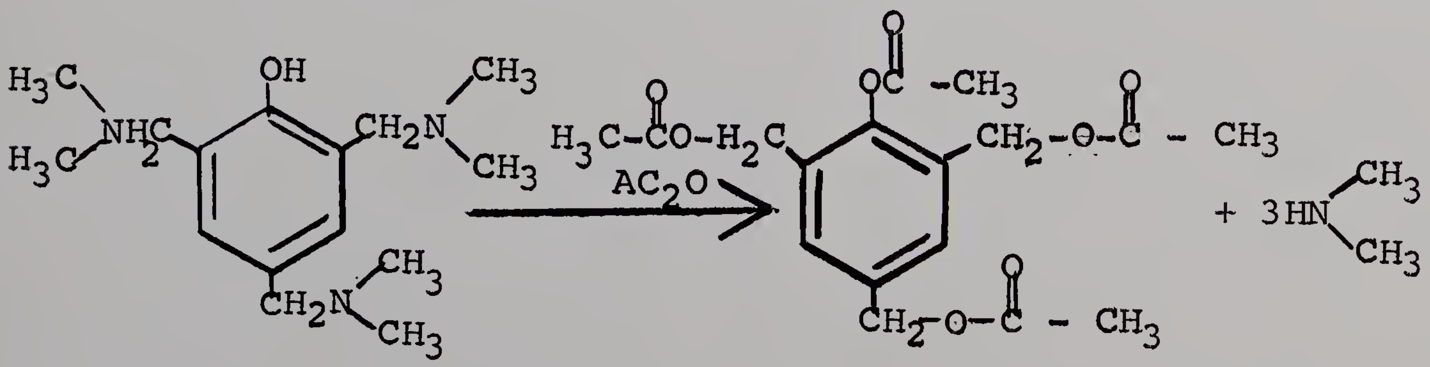


The ortho and para hydrogens in phenols are sufficiently active to enter into Mannich reaction. Thus condensation products from phenols (59), meta cresols (59), 3, 5-dimethylphenol (60), 4-methoxyphenol (61), β-naphthol (61), and 8-hydroxyquinoline (1) with formaldehyde and amines have been reported.

The products obtained by the Mannich reaction with phenols have possible synthetic uses in the introduction of methyl groups into the phenolic ring. Thus α-dimethylaminomethyl xylenol is readily hydrolized to 2,3, 5-trimethylphenol (60).



It has also been demonstrated that when these phenolic Mannich bases are treated with acetic anhydride, the dimethylamino groups are replaced by acetoxy groups (59).



It is important to note that one of the phenolic Mannich bases has been found to be effective against trophozite induced chick malaria (62). The carbamyl esters of 2-dialkylaminomethyl 3-pyridol prepared by Mannich reaction of 3-pyridol, formaldehyde and dialkylamine followed by esterification with carbamyl chloride have been found to have a pronounced parasympathomimetic action (63). They also find usage in intestinal activity, cholin esterase inhibition and as anticurare agents (64). These compounds have the added advantage of high stability.

THE STATEMENT OF THE PROBLEM

The wide-spread usage and importance of the Mannich reaction in the synthesis of organic medicinal agents is evident from literature survey. Many compounds can be synthesized through this method which otherwise might not be readily available. These include substances which possess antispasmodic activity or one or more of several pharmacological properties such as local anaesthetic action, antiparkinson activity, antimalarial activity, analgesic activity, antibacterial activity, etc.

The purpose of this dissertation is to investigate the synthesis of some new Mannich bases utilizing various amine - acyl combinations. It is expected that many of these compounds would prove to be very important intermediates for the synthesis of 8-azasteroids and potentially active antidiarrhoeal agents. In addition, the effect of steric factors will be considered and their influence on the course of the reaction well assessed.

In order to determine whether physical factors might be correlated with pharmacological activity, mass spectroscopy and infrared spectroscopy have been employed to study the compounds. In addition, spectroscopic methods have been used to elucidate the structures of the compounds reported in this dissertation.

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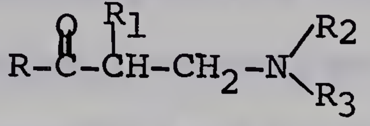
The purpose of this dissertation is to investigate the synthesis of some new Mannich bases utilizing various amine - aryl combinations. It is expected that many of these compounds would prove to be very important intermediates for the synthesis of 4-quinazolones and potentially useful chemotherapeutic agents. In addition, the effect of steric factors will be considered and such influence on the course of the reaction will be discussed.

In order to determine whether physical factors might be correlated with pharmacological activity, mass spectroscopy and infrared spectroscopy have been employed to study the compounds. In addition, spectroscopic methods have been used to elucidate the structures of the compounds reported in this dissertation.

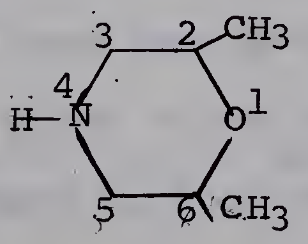
RESULTS AND DISCUSSION

In their studies, on the synthesis of antispasmodics by Mannich reaction, Denton and his co-workers (21) observed that the most effective amino group, in this series of compounds with the following general formula:-

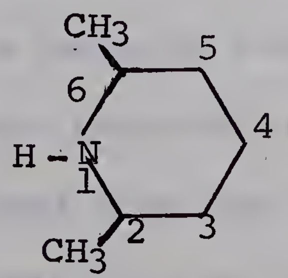


$$R-\overset{O}{\overset{\|}{C}}-\overset{R_1}{\overset{|}{C}}H-CH_2-N\begin{smallmatrix}R_2\\ R_3\end{smallmatrix}$$

was piperidyl. Compounds containing this amine moiety possessed outstanding properties when the acyl group belonged to the propiophenone series which possessed no ring or side-chain substituents. In addition, piperidyl was as effective as any other amino group in the propionaphthone series. On the other hand, morpholinyl derivatives were the least active. In addition, McElvain(65) observed that 2-methylpiperidinopropylbenzoate (Metycaine[R]) was a more active anaesthetic than piperidinopropylbenzoate. Although the relation between chemical structure and antispasmodic activity in the morpholino group has been studied very extensively, the effect which the introduction of methyl groups in the morpholine moiety has on antispasmodic activity of such compounds is unknown. A survey of literature failed to reveal any previously published use of 2,6-dimethylmorpholine as an amine moiety in the Mannich reaction.



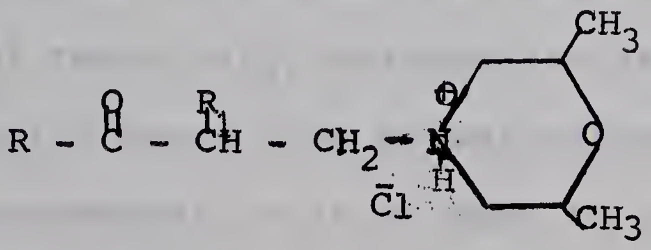
2,6-Dimethylmorpholine



2,6-Dimethylpiperidine

In view of the foregoing observations, interest in this type of work was stimulated. Therefore it was planned to synthesize a number of new Mannich bases in which 2,6-dimethylmorpholine formed a part.

2,6-dimethylmorpholine (boiling point 144-146°C) was transformed into its hydrochloride by passing dry hydrogen chloride gas through a solution of 2,6-dimethylmorpholine in ether. The resulting salt was very hygroscopic, and did not have a sharp melting point. Mannich bases of the type represented by the following general formula,

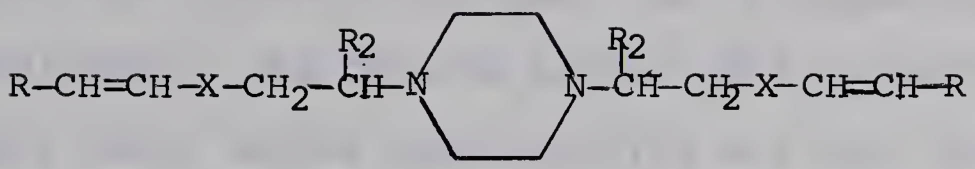


were synthesized by method A (1) as outlined in the experimental section. Generally, the compounds so obtained had sharp melting points and were not hygroscopic. Where the melting points were not sharp, the compounds were recrystallized from a mixture of ethanol and acetone. Seven new Mannich bases were synthesized using substituted acetophenones in which the substituents on the benzene ring were mainly in the meta or para position. No more than one substituent was introduced on the benzene nucleus at any time, since it had previously been reported (18) that considerable loss of antispasmodic activity resulted from the introduction of more than one substituent. According to Casadio et al (66)

the naphthalene derivatives of α, α-disubstituted acetonitriles are more interesting than the corresponding benzene compounds from the stand-point of antispasmodic activity. Therefore, methyl α-naphthyl ketone was used along with paraformaldehyde, and 2,6-dimethylmorpholine hydrochloride to obtain a new Mannich base. The report of Denton et al (21) that branching of the side chain resulted in an increase in antispasmodic activity in the morpholinyl compound prompted the use of propiophenone in the Mannich reaction employing 2,6-dimethylmorpholine as an amine moiety.

As the vinylogues of ketones are known to have similar chemical reactivity, Burckhalter and Johnson (40) synthesized Mannich bases from benzalacetone as vinylogues of β-aminopropiophenones in an attempt to enhance the analgesic effect of the latter. These bases, though devoid of analgetic activity, possessed antibacterial action in vitro. This unexpected behaviour of the vinylogues of Mannich bases initiated studies of the vinylogous concept to Mannich bases derived from 2,6-dimethylmorpholine hydrochloride. In the present study, the benzalacetone used was prepared from benzaldehyde and acetone in the presence of sodium hydroxide according to the procedure given in organic synthesis (67).

Coppi (68) studied the synthesis and pharmacological evaluation of alkyl piperazine salts and observed that alkyl piperazine esters of the type:-



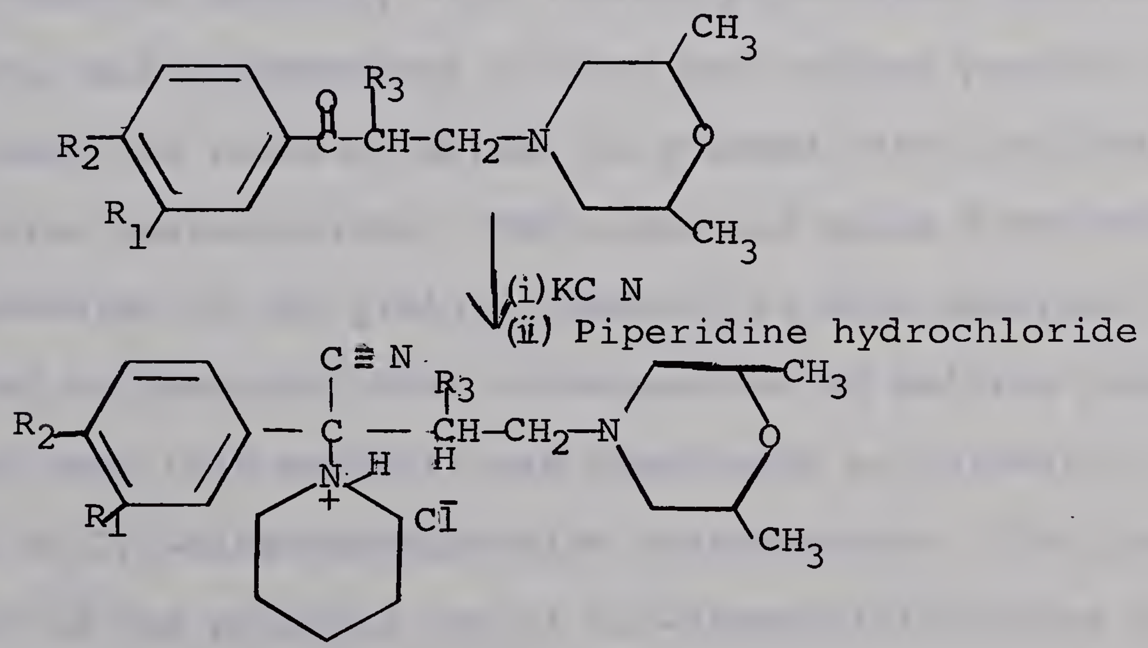
where $X = -\overset{O}{\overset{\|}{C}}-O$ showed anti-inflammatory, analgesic, antipyretic, antibacterial and antifungal properties. In view of the broad spectrum of activity of this type of compound, the synthesis of the new Mannich base of the above type where R is phenyl, X is keto, and R_2 is hydrogen was successfully achieved through the Mannich reaction from benzalacetone, formaldehyde, and piperazine dihydrochloride, using Method A. The piperazine dihydrochloride used in this synthesis was prepared in quantitative yield by passing dry hydrogen chloride through a solution of piperazine in acetone.

β-2,6-Dimethylmorpholinoethyl methyl ketone hydrochloride was synthesized from acetone, paraformaldehyde, and 2,6-dimethylmorpholine hydrochloride. This type of compound, it was hoped on reduction and subsequent benzoylation, would furnish a product which would prove to possess potent anaesthetic properties similar to a compound prepared from the morpholine moiety (30).

The occurrence of the furan ring system in a number of medicinal agents as well as the wide spread appearance of Mannich bases in medicine makes it particularly attractive to combine both features in a single structural unit. In

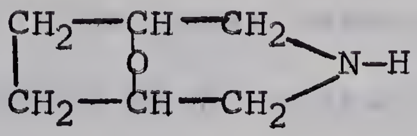
order to achieve this objective, 2-acetylfuran was allowed to react with paraformaldehyde, and 2,6-dimethylmorpholine hydrochloride. The desired product β-2,6-dimethylmorpholinoethyl furyl ketone hydrochloride was thus obtained in only 7% yield. It is note-worthy that the elemental analytical data of this compound is correct only if it is considered to contain half a molecule of water per mole. The presence of water was confirmed by the appearance of a peak at 3350 cm^{-1} in the infrared spectrum of this compound.

Furthermore, it was hoped that the Mannich bases prepared in this investigation would serve as important intermediates for the synthesis of compounds of the type illustrated by the following sequence of reactions:-



Synthesis of these compounds could be accomplished by stirring the Mannich base with potassium cyanide and piperidine hydrochloride at room temperature (69). The resulting compounds

would appear to possess interesting possibilities as antiperistaltic agents (70) and/or analgesics (66). In addition, successful use of substituted morpholines opens an avenue for the use of 8-oxa-3-azabicyclo (3.2.1) octane (71) which has fused tetrahydrofuran and morpholine rings.



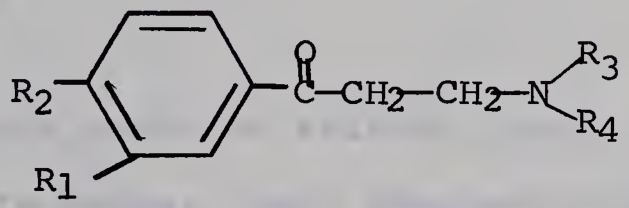
This would provide an interesting addition to the study of correlating the structure of Mannich bases with antispasmodic activity.

The synthesis of Mannich bases were also attempted using 3-methylpiperidine, and 2,6-dimethylpiperidine hydrochlorides. It is interesting to note that, while the reaction proceeded smoothly with 3-methylpiperidine, paraformaldehyde, and acetophenone to give the desired product in 81% yield, the reaction failed to proceed with 2,6-dimethylpiperidine hydrochloride. The unreacted amine hydrochloride was recovered in 70% yield. Identity of this material was verified by observing that no depression of melting point occurred when this material was mixed with an authentic sample of 2,6-dimethylpiperidine hydrochloride. The investigation of the possible use of 2,6-dimethylpiperidine hydrochloride was attemtpted since it is assumed that no fundamental change in pharmacological activity will result from opening the five membered ring of ecgonine or tropine in such a manner that, in place of both methylene groups, two

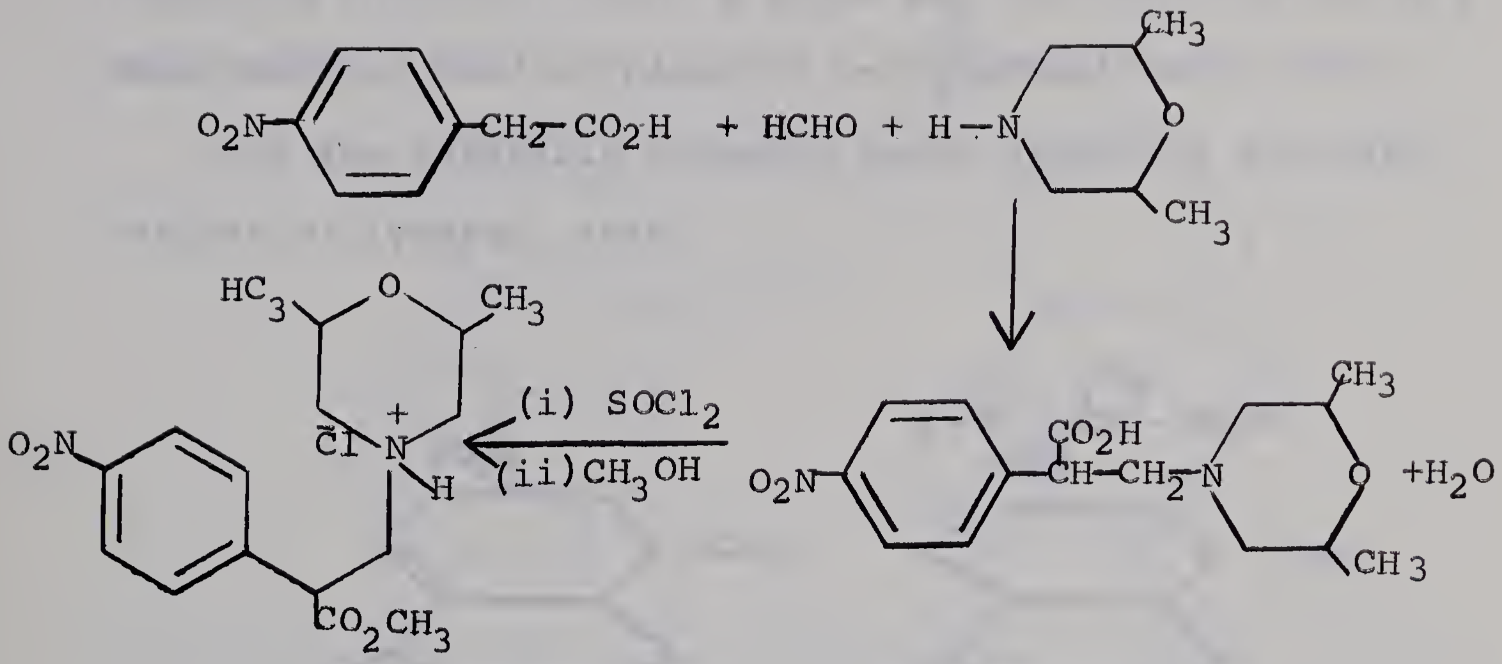
methyl groups are introduced (49).

Ten Mannich bases were also synthesized using morpholine and piperidine hydrochlorides as amine moieties (eight of these compounds are known in literature) in order to make certain generalizations regarding their antispasmodic activities from their mass-spectra.

Although Mannich bases containing the morpholine ring in compounds of the type,

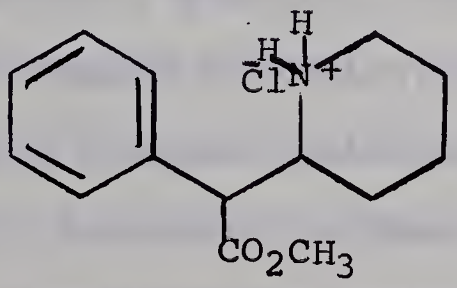


are known to possess low antispasmodic activity, however, basic esters containing morpholine ring have pronounced activity and in general, are less toxic than their diethylamine analogues (72). Therefore, the synthesis of β-amino esters using 2,6-dimethylmorpholine was achieved through the esterification of the corresponding β-amino acid by method D. (73). The acid, however, was synthesized from para nitrophenylacetic acid, formaldehyde solution (37%), and 2,6-dimethylmorpholine through the Mannich reaction using method C. (74).



The β-amino acids exist as zwitter ions. Since zwitter ions are usually rather inert pharmacologically (75) no special attempt was made to purify the acid.

The salt of the β-amino ester of the type synthesized through the previous sequence of reaction, in addition to being antispasmodic, may have pharmacological properties similar to that of methylphenidate hydrochloride (76).

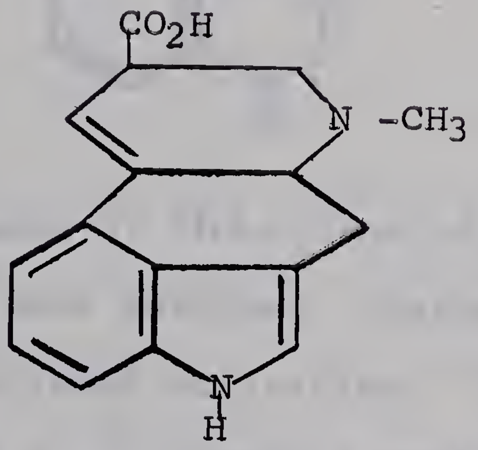


Methyl phenidate hydrochloride

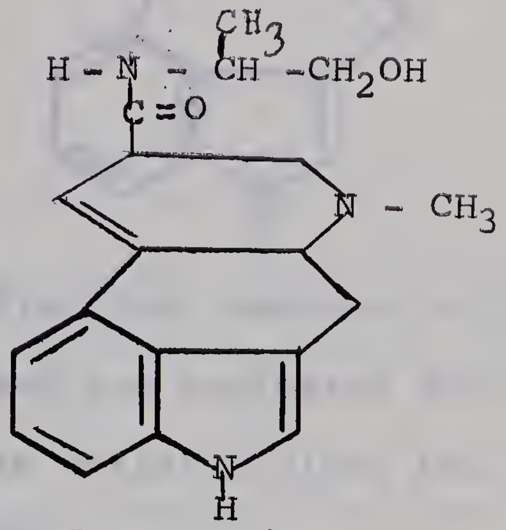
The presence of nitro group in the compounds synthesized in this project may increase their toxicity.

Compounds without the nitro group may be obtained by using phenylmalonic acid in place of p-nitrophenylacetic acid.

All the naturally occurring ergot alkaloids are derivatives of lysergic acid.

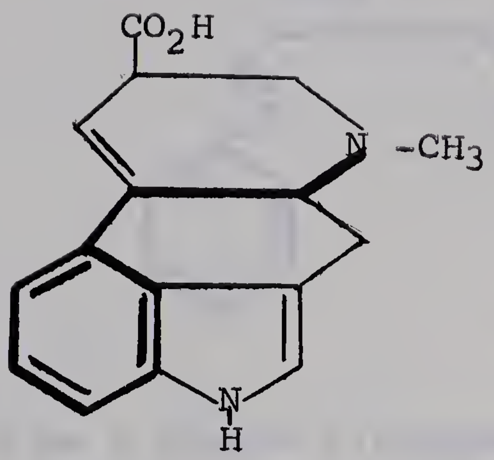


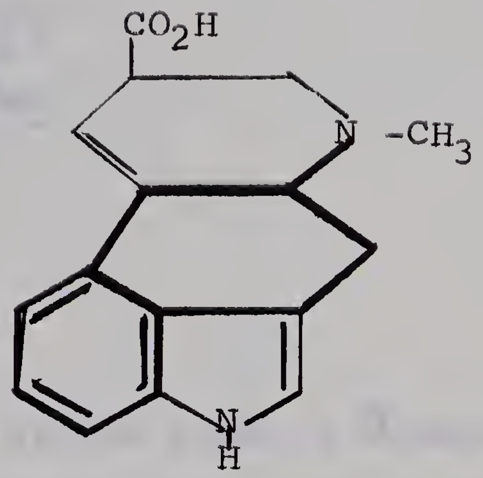
Lysergic Acid



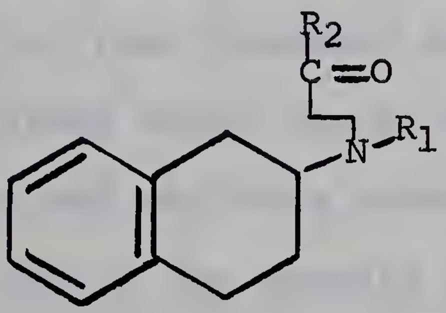
Ergometrine

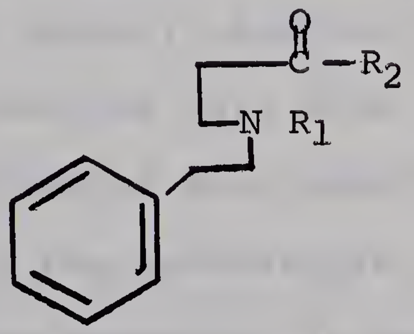
They have been widely used as (1) oxytocics (2) vasoconstrictors and (3) spasmolytics (77). Bovet and co-workers (78) through the ingenious design of a series of analogues, utilizing the method of disjunction, have given an answer to the very important question, whether the three actions of these alkaloids depend on a single pharmacomorphic moiety or whether there are distinct moieties responsible for each type of action. According to them, these actions are separable. They visualized the presence of a sympathomimetic amine structure embedded in the lysergic acid nucleus as follows:-



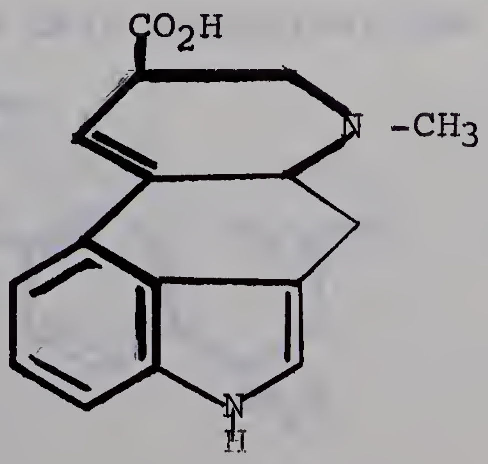


On the basis of this type of reflection, various series of products were designed, synthesized and evaluated for the above mentioned activities. These series include the following types of disjunction analogues:-

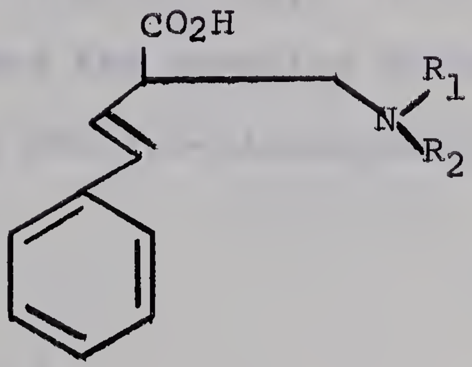




where R_1 = various alkyl groups; R_2 = various alkyl amide groups. Careful examination of lysergic acid molecule shows the presence of another type of structure.

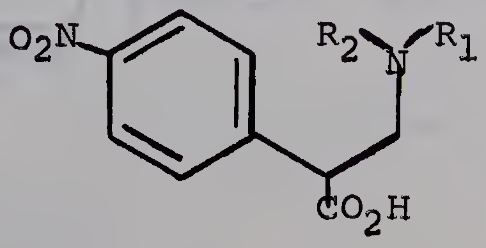


Upon rewriting the delineated portion separately, it is

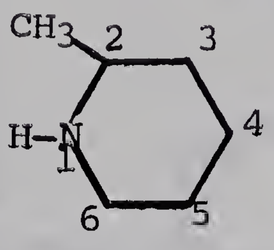


observed to be a simple vinylogue of the type of β-amino acid which has been synthesized by Mannich reaction (74). Therefore, derivatives of β-amino acids synthesized thus far may be expected to be potentially active.

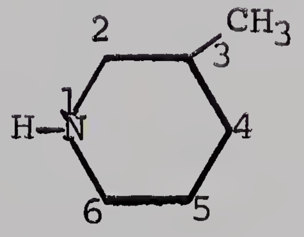
One of the problems in steroid therapy is caused by their low water solubility. As a result, when adminstered orally, poor systemic absorption occurs. Azasteroids on the other hand, can be easily converted into water soluble salts and may thus prove more effective at a lower dosage. In view of the general utility of the azasteroids, an easy approach to the synthesis of these compounds is desirable. In order to synthesize the 8-azasteroidal skeleton via Mannich reaction, information about the possible usage of substituted piperidines as amine moieties was needed. In order to achieve this objective, the synthesis of Mannich bases of the type,



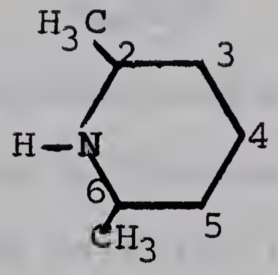
was attempted using 3-methylpiperidine, 2-methylpiperidine, 2,6-dimethylpiperidine and 2,6-dimethylmorpholine. It was noted that whereas the reaction proceeded smoothly with 3-methylpiperidine and 2,6-dimethylmorpholine, it failed to proceed



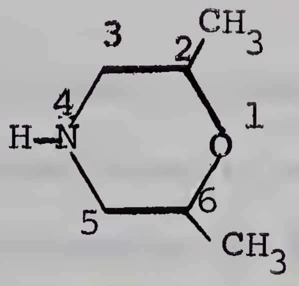
2-Methylpiperidine



3-Methylpiperidine

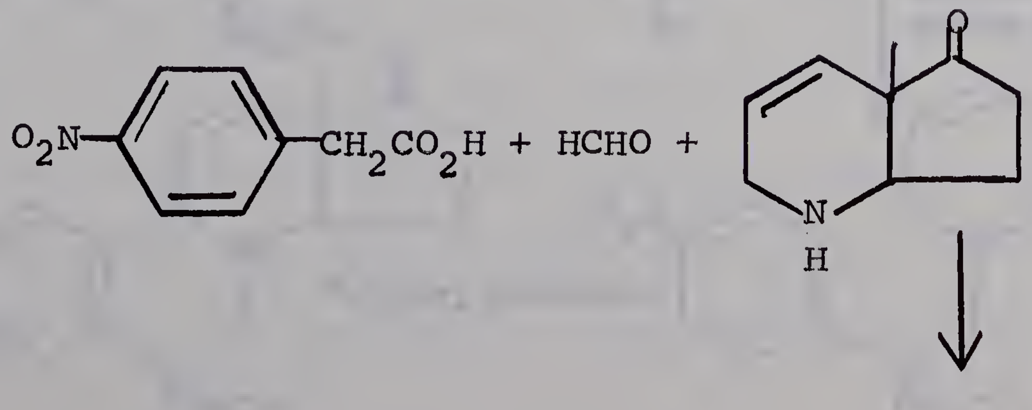


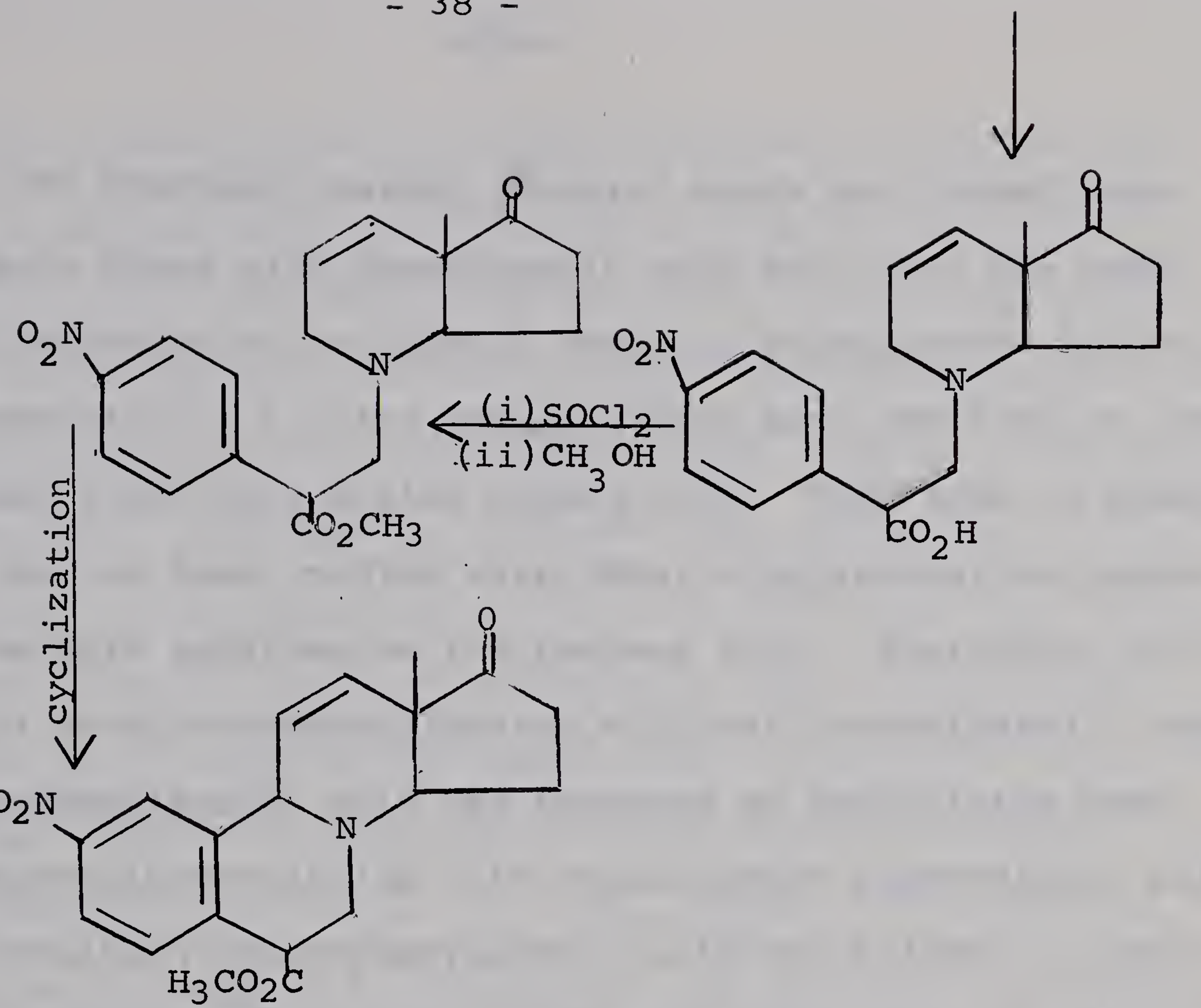
2,6-Dimethylpiperidine



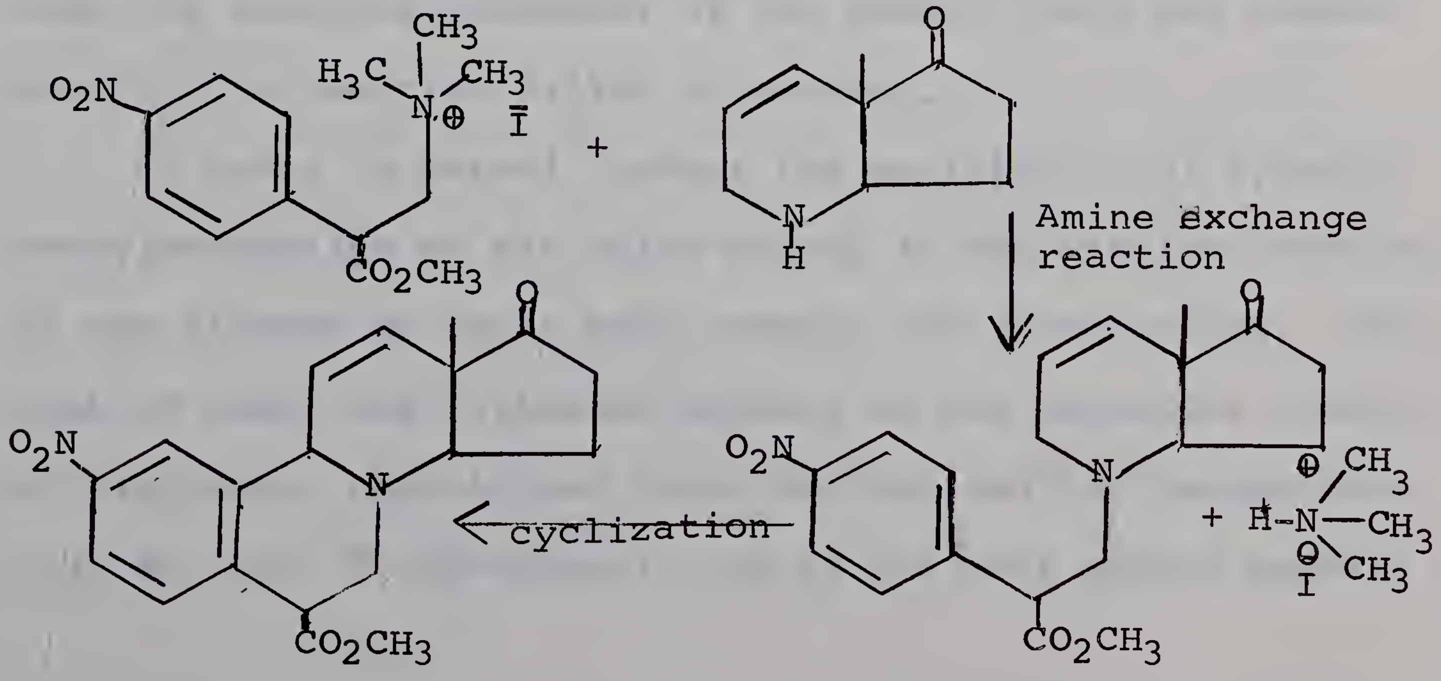
2,6-Dimethylmorpholine

with 2,6-dimethylpiperidine and 2-methylpiperidine. This shows that the objective aimed at the synthesis of 8-aza-steroids through Mannich reaction cannot be achieved by the previously postulated scheme:-





β-Dimethylamino-α-p-nitrophenylpropionate hydrochloride was synthesized from p-nitrophenylacetic acid, formaldehyde solution (37%), and dimethylamine by Mannich reaction, followed by esterification. It is postulated that the methiodide of this compound would serve as an important intermediate for the synthesis of 8-azasteroids by amine exchange reaction (39) followed by cyclization.

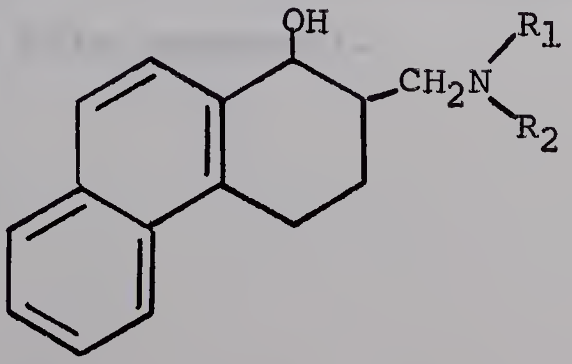


The reaction whereby β-amino acids are formed does not take place with phenylacetic acid but, when the negative character of the phenyl group is strengthened by the introduction of a nitro group, at the para position on the benzene ring the reaction occurs (74). This type of reaction has not been studied with other electronegative groups at the para position on the benzene ring. Therefore, the use of para chlorophenylacetic acid was investigated. Para chlorophenylacetic acid was prepared by hydrolizing para chlorphenylacetonitrile with concentrated hydrochloric acid. The resulting chlorophenylacetic acid was allowed to react with formaldehyde solution (37%) and piperidine by method C. No solid separated on heating the contents at 40°C for 24 hours, thus indicating that the reaction failed to proceed. In this instance, probably due to the presence of lone pairs of electrons, the chloro group instead of acting as an electrophilic agent, which could increase the negative character of the phenyl group, acted as an electron donor. This weakened the negative character of the phenyl group and consequently the reaction failed to proceed.

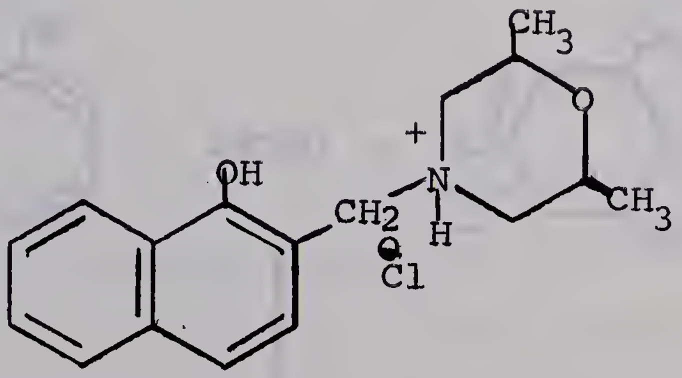
In order to extend further the application of 2,6-dimethylmorpholine as the amine moiety in the Mannich reaction, it was allowed to react with phenols and formaldehyde. This type of study was initiated because of the extensive utility of alkylamino phenols and their derivatives in therapeutics, (79, 80, 81). α-Tocopherol, one of the most potent members

of the vitamin E group has been prepared from phytol and pseudo cumohydroquinone. In view of the pharmacological activity of other derivatives of this latter compound, as well as the related quinones such as durohydroquinone, the desirability of other and simpler means of their synthesis is obvious. Caldwell and Thompson (60) attempted to synthesize pseudo cumohydroquinone by introducing three methyl groups directly into hydroquinone by means of the Mannich reaction, followed by hydrogenation. Analysis of the resulting compound revealed that it was the di(dimethylaminomethyl) derivative. In this present investigation, an attempt was made to synthesize 2,3,5-tri(2,6-dimethylmorpholinomethyl)-hydroquinone. One equivalent of hydroquinone was allowed to react with three equivalents each of formaldehyde solution (37%) and 2,6-dimethylmorpholine. The resulting sticky mass, upon recrystallization twice from anhydrous methanol, yielded a white crystalline solid m.p. 218-225°C. The analysis of this product showed that the resulting compound was di(2,6-dimethylmorpholinomethyl)-hydroquinone.

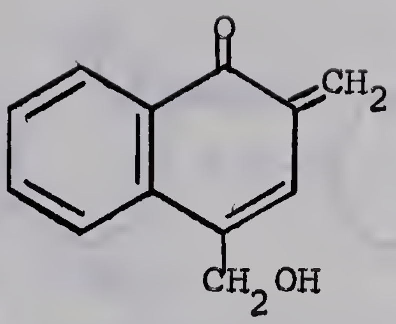
Mosettig and May (82) observed that the phenanthrylamino alcohols, the so called cyclic amino alcohols of the type,



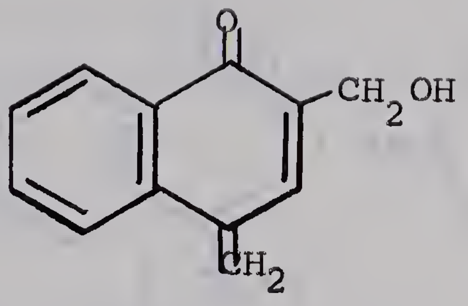
and their analogues "3,4 derivatives" were most promising as analgetic agents. Chemical and pharmacological investigations carried out by them indicated that the phenanthrene nucleus may not be essential in producing an analgesic action. These authors observed similar pharmacological properties with compounds containing the naphthalene nucleus. It appears possible that a certain arrangement of the functional groups attached to any ring skeleton of adequate size may bring about the desired pharmacological effects. Therefore, it was decided to prepare the following compound:-



starting from α-naphthol, formaldehyde, and 2,6-dimethylmorpholine hydrochloride through the Mannich reaction by means of method A. A new compound melting at 301-304°C was obtained. Its elemental analyses revealed that there was no nitrogen in the compound. On the basis of analyses, and the fact that peaks appeared at 1685, 1665 and 1630 $cm.^{-1}$ in the infrared spectrum, the following two structures were proposed for this compound:-

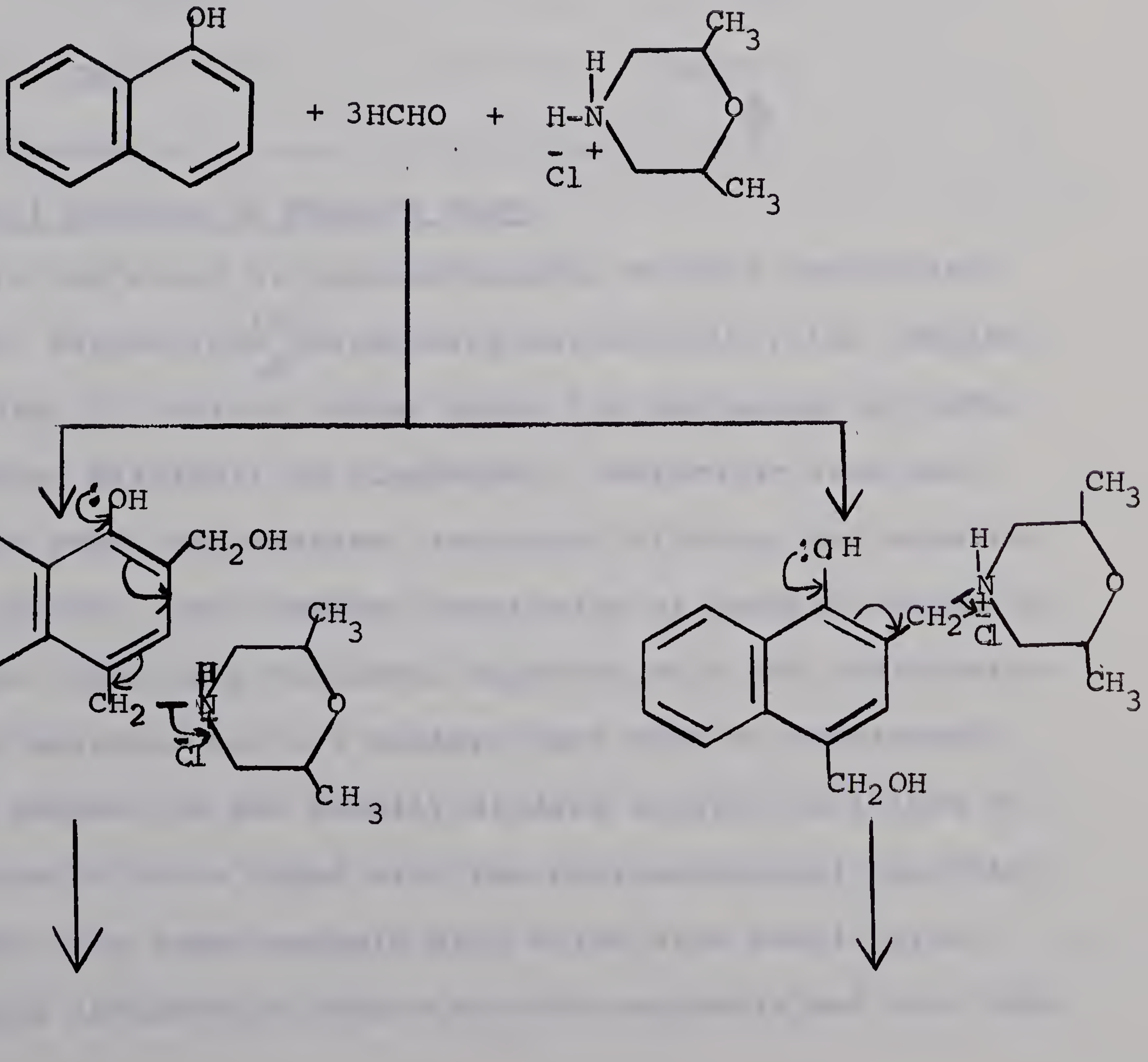


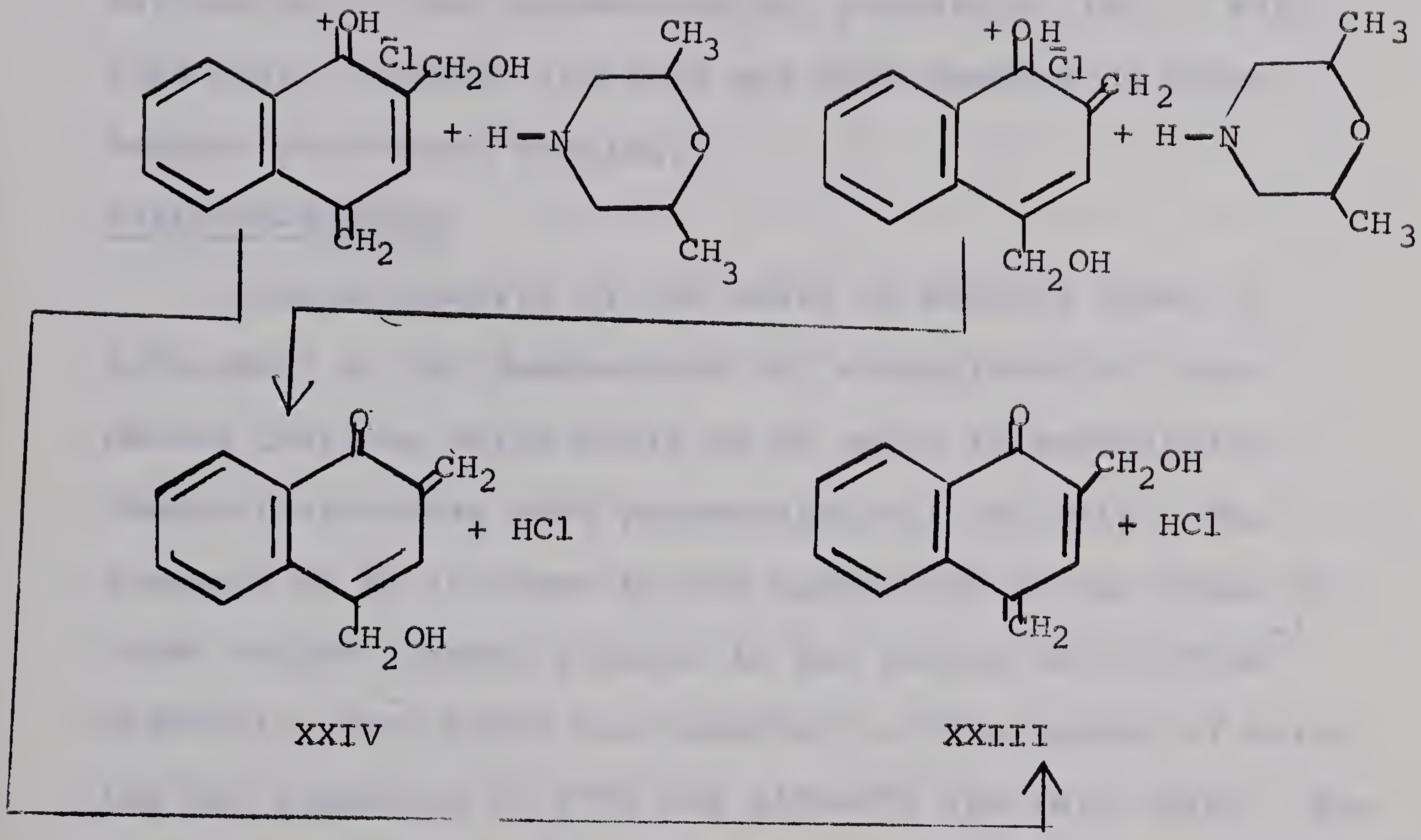
XXIII



XXIV

The structures suggested above may have been formed by the following mechanisms:-



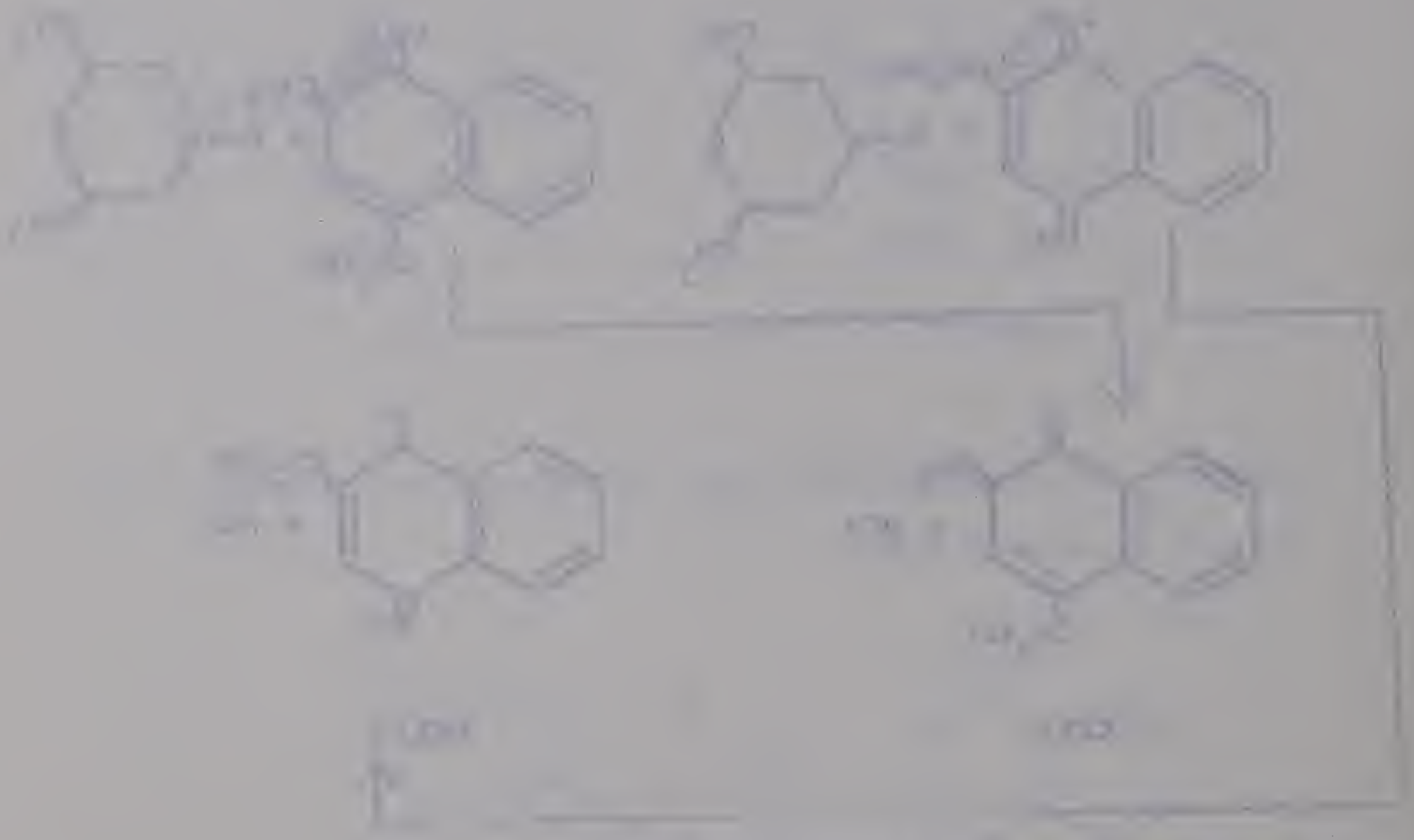


XXIV

XXIII

Spectral Studies of Mannich Bases

In the study of physicochemical factors associated with or responsible for pharmacological activity, the complex interplay of various forces makes the mechanism and mode of action difficult to comprehend. Molecular size and surface area, tautomerism, resonance effects, and electron distribution, the chemical reactivity of specific groupings and the intergroup distances together with the conformation of the molecule are all factors that must be considered. These properties are usually studied singly and little or no correlation is found with the pharmacological activity. However, the spectroscopic data which also result from multiple interaction both within the molecule and with the



Physical Methods of Studying Drugs

In the study of physicochemical factors associated with or responsible for the pharmacological activity, the complete [illegible] of multiple factors [illegible] has been [illegible] and that of [illegible] significance to [illegible]. [illegible] data and solubility data, thermochemical, [illegible] methods, and electron distribution, the chemical reactivity of specific groupings and the [illegible] distribution [illegible], the [illegible] of the molecule [illegible] all become tools that help in such studies. These properties are usually studied singly and little is of correlation is found with the pharmacological activity. However, the spectroscopic data which also [illegible] [illegible] with the molecule and [illegible]

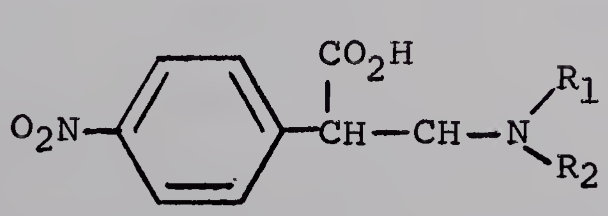
molecular environment might be expected to bear some relationship to the pharmacological properties (83). With this point in view, infrared and mass-spectra of these Mannich bases were studied.

Infrared-Spectra

Infrared-spectra of the salts of Mannich bases in nujol-mull do not demonstrate any exceptional or unexpected features which would be of value in correlating chemical structure with pharmacological activity. The presence of $\overset{+}{N}H$ is shown by the appearance of one broad or three or four separate peaks in the region 2670-2350cm^{-1}. Generally, four peaks are observed in this region of which the two appearing at 2550 and 2470cm^{-1} are very sharp. The other two peaks are present as shoulders at 2690 and 2350cm^{-1}. The assignment of these peaks to $\overset{+}{N}H$ was confirmed by the absence of these peaks in the infrared spectra of the corresponding free bases. The carbonyl group appears at about 1690cm^{-1}. The position of this peak remains unchanged in the corresponding free bases. However, the position of this carbonyl peak increases to a higher value with the introduction of electron attracting groups and decreases to a lower value with the introduction of electron donating groups on the aromatic nucleus. In addition, when the side-chain is branched by the introduction of an electron donating group, the carbonyl peak again shifts to a lower position. However, in α,β-unsaturated ketonic Mannich bases, two peaks

appear at 1665 and 1625cm^{-1}. The presence of phenyl group is demonstrated by the appearance of peaks at 1600 and 1580cm^{-1}. When the phenyl group has five adjacent carbon atoms, peaks appear at 1460, 745 and 695cm^{-1}. The presence of para substituted benzene compounds is easily detected by the appearance of four to five peaks in the 860-800cm^{-1} region. The meta substituted aromatic compounds exhibit peaks in 910-860 and 805-735cm^{-1} regions, which show the presence of one and three adjacent hydrogen atoms respectively on the benzene ring. When the nitro group is present on the benzene ring, peaks appear at 1535 and 1350cm^{-1}, which is assigned to $=C-NO_2$. The appearance of peaks at 1260 and 1225cm^{-1}, result from the presence of alkoxy groups on the benzene ring. The most characteristic peak of furan appears at 800cm^{-1}, Where 2,6-dimethylmorpholine is the amine moiety, a very characteristic peak appears near 1087cm^{-1}, which is assigned to disubstituted diisopropyl ether ($>$CH-O-CH$<$).

Infrared spectra of the β-amino acids of the type:-



show peaks at νmax, 2500-1800($\overset{+}{N}H$), 1640(CO_2^-),1605(phenyl group), 1535 and 1340($=C-NO_2$), and 860-830(1,4-disubstituted benzene ring) cm^{-1}.

The salts of the β-amino esters show peaks in infrared

spectra at ν_{max}, 2530-2220 broad($\overset{+}{N}H$), 1737($-\overset{O}{\overset{\|}{C}}-$), 1600 (phenyl group) 1530 and 1343 ($=C-NO_2$), and 860-830(1,4-disubstituted benzene ring) cm^{-1}.

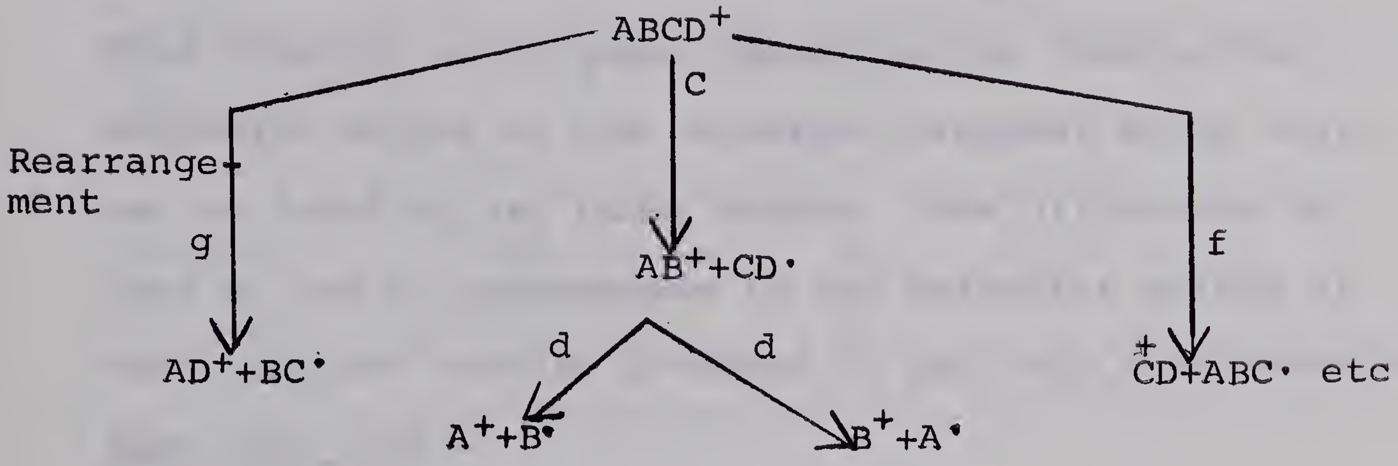
Mass Spectra of Mannich Bases:-

In recent years, the importance of mass spectrometry as a useful tool for structure determination has been well established. It has been extensively used only since 1960, and already results have been spectacular. As this field is relatively very new, a brief introduction to the principals of mass spectrometry will be given here to acquaint the uninitiated chemist with these principals, thus enabling him to appreciate the technique as a useful tool for structure elucidation of organic compounds.

The sample to be analysed is placed in the sample reservoir from where it is brought to the ionization chamber by heating the sample under reduced pressure. In the MS-9 mass spectrometer, the sample can be placed directly into the ionization chamber by direct probe introduction method. An electron gun is then switched on for a few nano seconds. When the electron beam strikes the molecule, a molecular ion is formed by a loss of a valence electron. The positive ion so obtained is known as the parent ion, or molecular ion. The detection of this peak in the mass spectrum is of great importance as it gives the exact molecular weight of the compound. Electrons of higher energy are able to transfer more energy to the molecule which may then decompose into fragments by bond cleavage. This process may occur in more than one step. A very useful general scheme has been postulated by Biemann(84) for the fragmentation of a hypothetical molecule:-

Ionization (a) $ABCD + \bar{e} \longrightarrow \overset{+}{ABCD} + 2\,\bar{e}$

Decomposition (b) $ABCD^{+} \longrightarrow A^{+} + BCD^{\bullet}$



Ion molecular collusion:-

$$(h)\ ABCD^{+} + ABCD \longrightarrow \left[ABCD\cdot ABCD\right]^{+}$$
$$\downarrow$$
$$\left[ABCD\cdot ABCD\right]^{+}$$

The number of decomposition reactions of type (b-g) is considerable and leads to the large number of peaks in the mass spectra. The intensities of these peaks are, however, of importance since they are dependent on the probability of formation of the individual fragments.

Metastable peaks (85):-

Sometimes, a broad low intensity peak is observed in the spectrum and it is so characteristic that it can never be mistaken for a normal peak. This peak is produced when an ion m_1 decomposes in the accelerating region of the mass spectrometer to another ion m_2 and an uncharged fragment. This peak can be related to the

parent ion m_2 by the simple relationship

$$\text{metastable ion } m^* = \frac{m_2^2}{m_1}$$

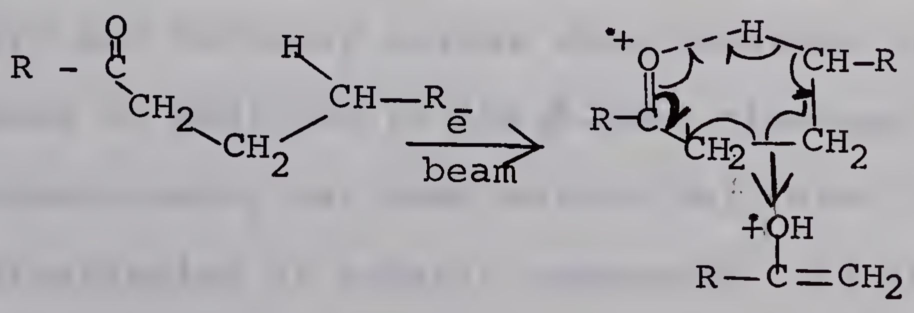
This relation is of great importance in finding the molecular weight of the uncharged fragment which could not be found by any other method. The difference in ions m_1 and m_2 corresponds to the molecular weight of the uncharged species produced in one step fragmentation.

Base Peak (86):-

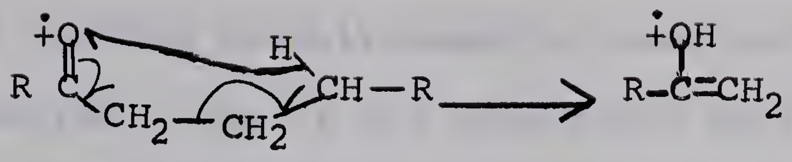
The largest peak in the spectrum is called the base peak. This peak is assigned a value of 100% and the other peaks are reported as a percentage of the base peak.

Electron shifts in mass spectrometry (87):-

The mechanism of formation of peaks or fragments is shown by the electronic shifts. These electronic shifts are denoted by  showing the movement of one electron in place of usual two electron shifts  which are common in other reaction mechanisms. The usage of one electron shifts may be depicted as follows:-



but for the sake of simplicity the mechanism is generally written as:-



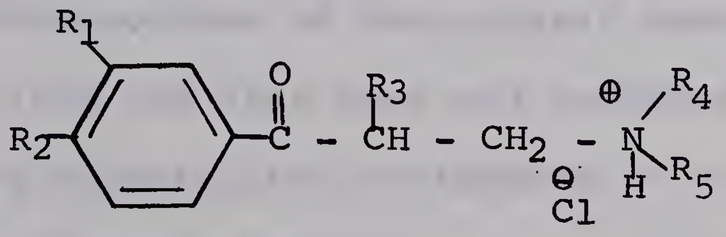
General rules for the formation of the fragmentation ions (88, 89, 90):-

The probability of cleavage of a particular bond is related to the bond strength. Some of the general rules for predicting the prominent peaks in the spectrum are:-

1. The cleavage is favoured at branched carbon chain.
2. Double bonds favour allylic cleavage.
3. Saturated rings favour cleavage of α-bond.
4. Aromatic compounds favour cleavage of β-bond.
5. Compounds containing heteroatoms favour cleavage of β-bond to a heteroatom.
6. McLafferty rearrangement involving six membered cyclic transition state is of importance in aliphatic ketones and nitriles having hydrogen in γ-position.
7. Primary amides favour cleavage of β-bond to carbonyl group accompanied by rearrangement of hydrogen atom to the fragment containing the nitrogen atom.
8. Secondary and tertiary amides show cleavage of the $-\overset{O}{\overset{\|}{C}}-$ N bond in addition to the β-bond cleavage.

Mass spectroscopy has been extensively used for the structure elucidation of organic compounds. As an investigational tool, however, this technique has not been applied to the solution of problems posed by structure-activity correlation. Whether the mass spectral data can be

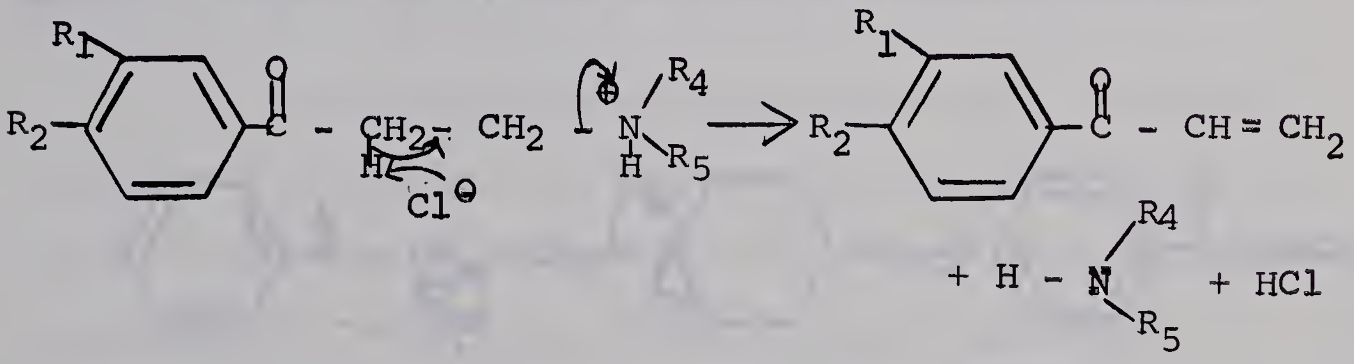
employed for the establishment of such correlations is an open question. One of the objections that may be raised against the establishment of such relationships through mass spectral data is that the conditions under which the spectra are recorded differ entirely from the conditions existing in the body. On the other hand, as the fragmentation pattern in mass spectra depends on the relative bond strengths, the intensities of the peaks in the mass spectra may give some idea about the bond strengths of the organic compounds. This knowledge of relative bond strengths may subsequently be used in establishing structure-activity relationship. The published data on the mass spectral behaviour of the hydrochloride salts of organic compounds are few. The literature survey did not reveal any publication dealing with the cleavage pattern of hydrochlorides of Mannich bases of the type,



hence it was decided to study the mass spectra of these types of compounds in which the amines used were morpholine and piperidine hydrochlorides. It was intended to apply the knowledge thus obtained to predict the activities of the new untested Mannich bases.

For β-piperidinoethyl phenyl ketone hydrochloride, prominent peaks of interest in the mass spectrum were noted at m/e 132, 105, 98, 85, 84, 77, 70, 57, 56, 51, 43 and 42. The formation of these peaks could be explained by the following mechanisms:-

The first possibility is that a Hofmann type of elimination may take place at the high temperature used to obtain the spectra.

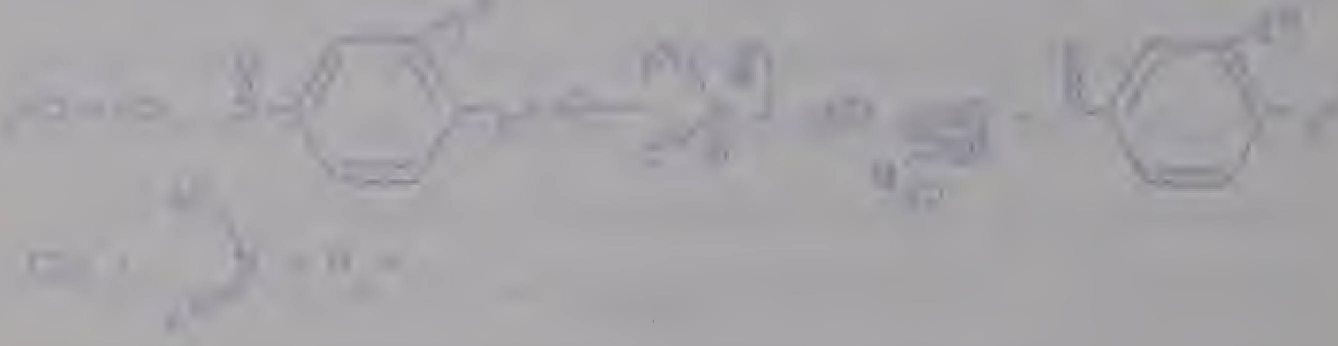


The resulting compounds then enter the ionization chamber independent of each other and this results in the ions observed in the spectra. This type of mechanism is not supported in the literature as it has been reported (91) that hydrochlorides of the organic bases dissociate on heating into the free base and hydrogen chloride, and the resulting spectra thus correspond to a superposition of these two components.

In order to determine the validity of this viewpoint, the free keto base, β-piperidinoethyl phenyl ketone, was prepared from the corresponding hydrochloride and the mass spectrum obtained. It may be mentioned here that the free bases were introduced through the heated inlet system whereas the corresponding hydrochlorides were

The β-piperidinoethyl phenyl ketone hydrochloride, prominent peaks of interest in the mass spectrum were found at m/e 105, 127, 98, 86, 84, 77, 71, 55, 51, 41 and 29. The formation of these peaks could be explained by the following mechanisms:-

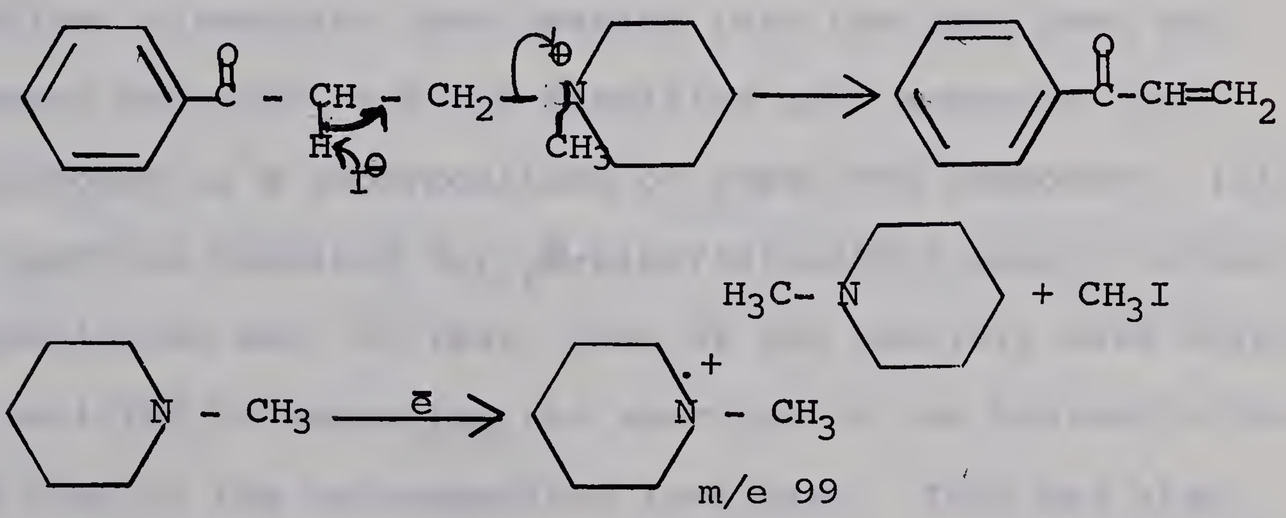
The first possibility is that a thermal type of elimination may take place in the high temperature inlet to produce the olefin.



The resulting components then enter the ionization chamber independent of each other and this results in the ions observed in the spectra. This type of mechanism is not supported in the literature as it has been reported that hydrochlorides of the Mannich bases dissociate by breaking into the free base and hydrogen chloride, and the resulting spectra then correspond to a superposition of these two components.

In order to determine the validity of this mechanism, the free base, β-piperidinoethyl phenyl ketone, was prepared from the corresponding hydrochloride and the mass spectrum obtained. It may be mentioned that the free base was introduced through the heated inlet system whereas the corresponding hydrochloride was

admitted by direct probe introduction method. The mass spectrum of the free base was found to be superposable on that of its hydrochloride. This showed that the Hofmann type of mechanism may not be correct. However, evidence supporting the Hofmann type of mechanism was provided by the mass spectrum of the corresponding methiodide. If this type of mechanism were correct, a peak should have appeared at m/e 99 by the following cleavage pattern:-



and actually a peak was observed at m/e 99(2%). Undoubtedly, objections could be raised against this evidence. Firstly, that whereas the methiodides of tertiary bases undergo Hofmann degradation very easily, the corresponding hydrochlorides have not been observed to participate in this reaction. Moreover, the breakage pattern of methiodides appears to be different from that of the corresponding free bases and the hydrochlorides. This was shown by the fact that, in β-piperidinoethyl phenyl ketone, peaks with m/e 85 and 84 were 28% and 53% respectively, and, in

the corresponding hydrochloride were 35% and 65% respectively, whereas, in the corresponding methiodide they were observed to be only 2% and 4% respectively.

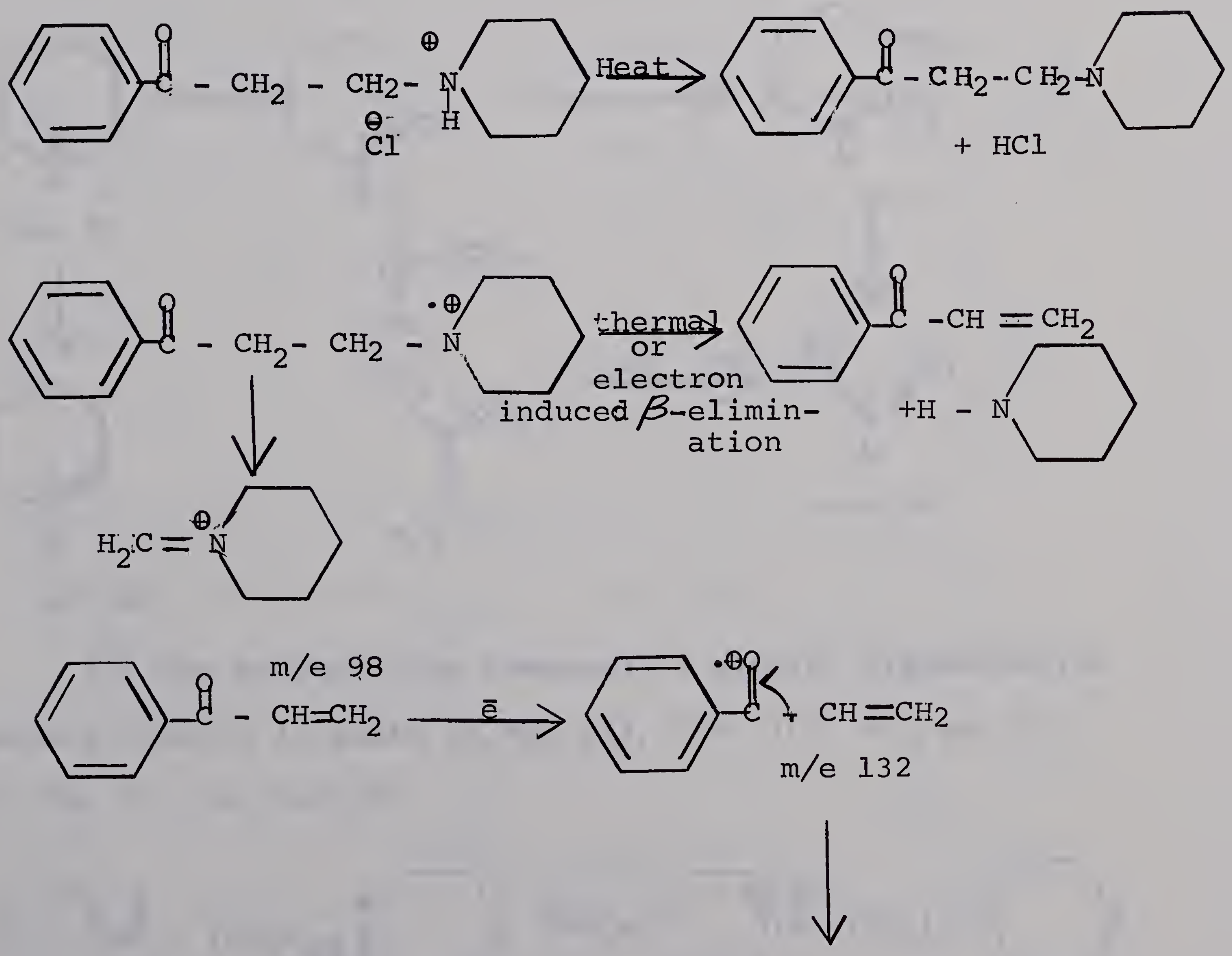
In addition, the appearance of peaks in β-piperidinoethyl phenyl ketone hydrochloride and β-morpholinoethyl phenyl ketone hydrochloride at m/e 98 and m/e 100 respectively provide strong evidence against the Hofmann type of mechanism.

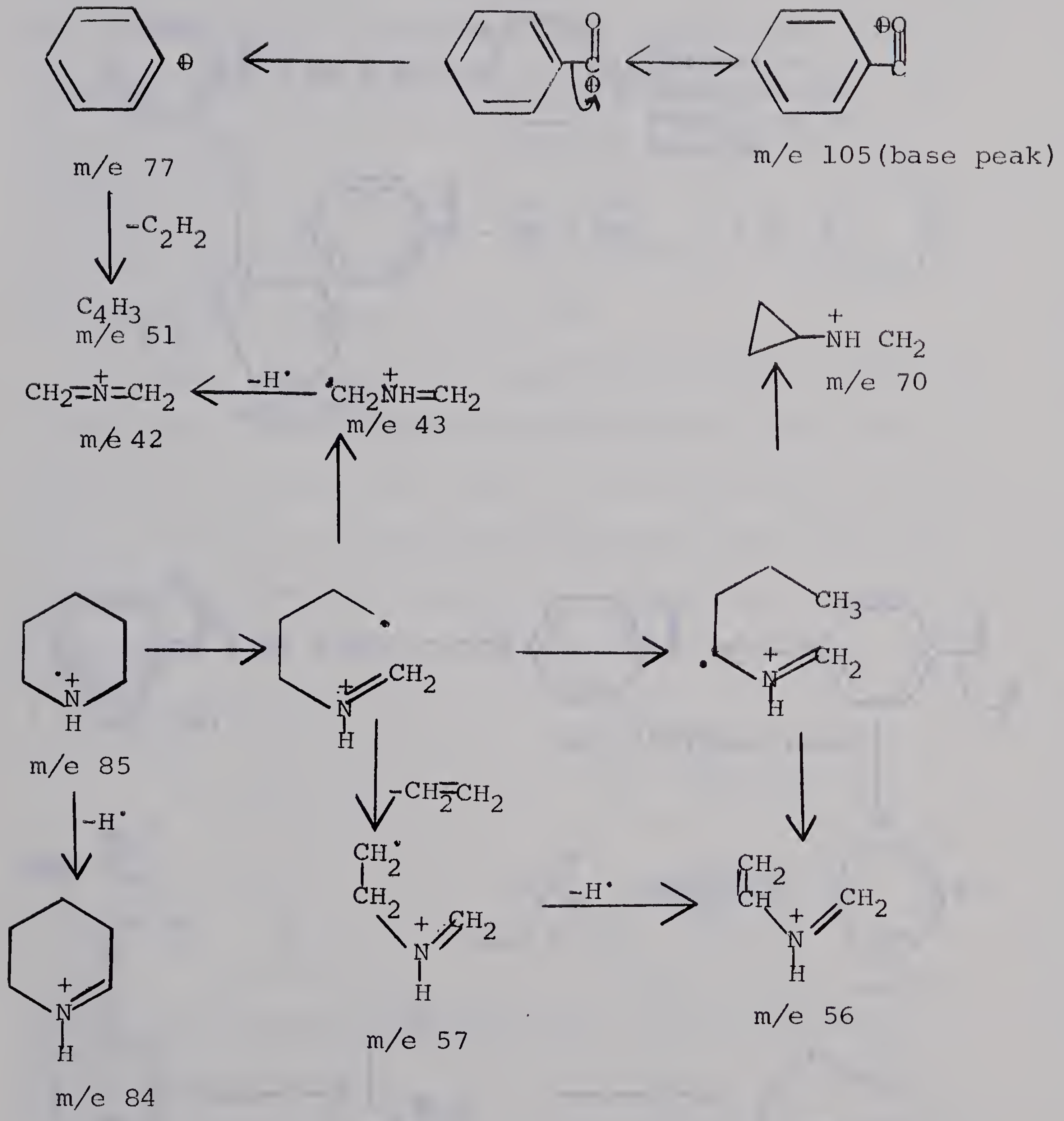
The second plausible mechanism is that the hydrochlorides dissociate upon heating into the free base and hydrogen chloride, and the resulting mass spectrum thus corresponds to a superposition of these two components (91). The spectrum obtained for β-piperidinoethyl phenyl ketone hydrochloride was, in fact, that of the tertiary base which was verified by comparing the spectrum of the hydrochloride with that of the corresponding free base. This was also confirmed by comparing the spectrum of β-2,6-dimethylmorpholinoethyl phenyl ketone hydrochloride with that of its free base.

If the above view-point is correct, peaks would also be expected at m/e 36 and m/e 38 ($H^{35}Cl$ and $H^{37}Cl$) but no peaks were observed at these m/e ratios. As a result of the low volatility of the compounds and the fact that an MS-9 mass spectrometer was used, and taking into account that the sample was admitted through a solids probe, it is likely, that the hydrochloride dissociated under the

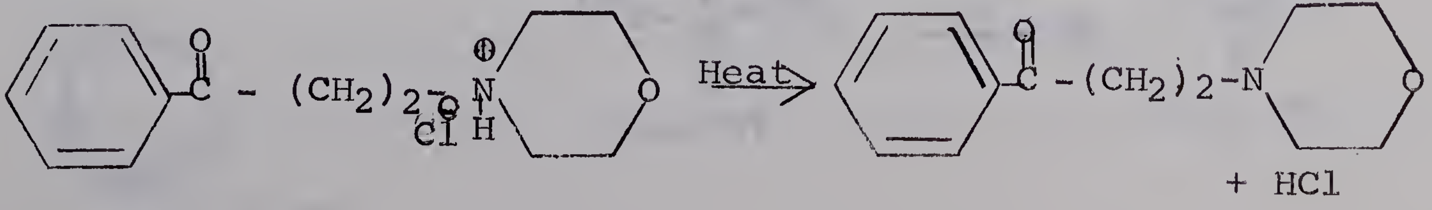
conditions of high vacuum and high temperature. Consequently, the spectra obtained were actually those of the free bases. This assumption is supported, in part, by the appearance of M-36 peaks in β-morpholinoethyl phenyl ketone and β-2,6-dimethylmorpholinoethyl phenyl ketone hydrochlorides.

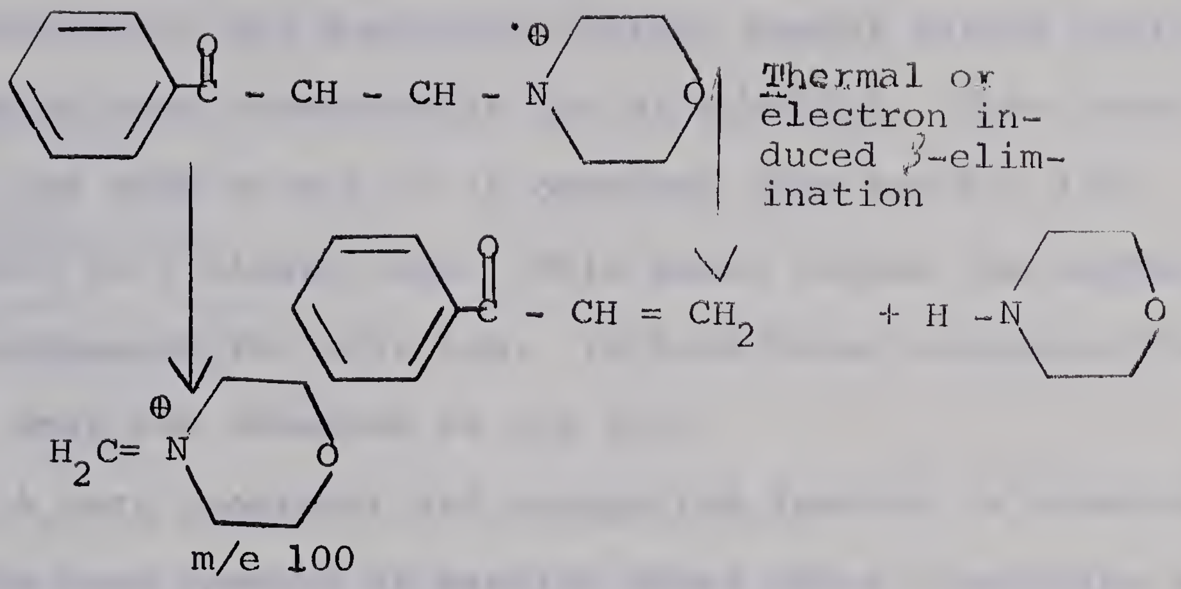
These β-amino ketones appear to undergo thermal or electron impact induced β-elimination to vinyl phenyl ketone and the amine which are the main features of the spectra.

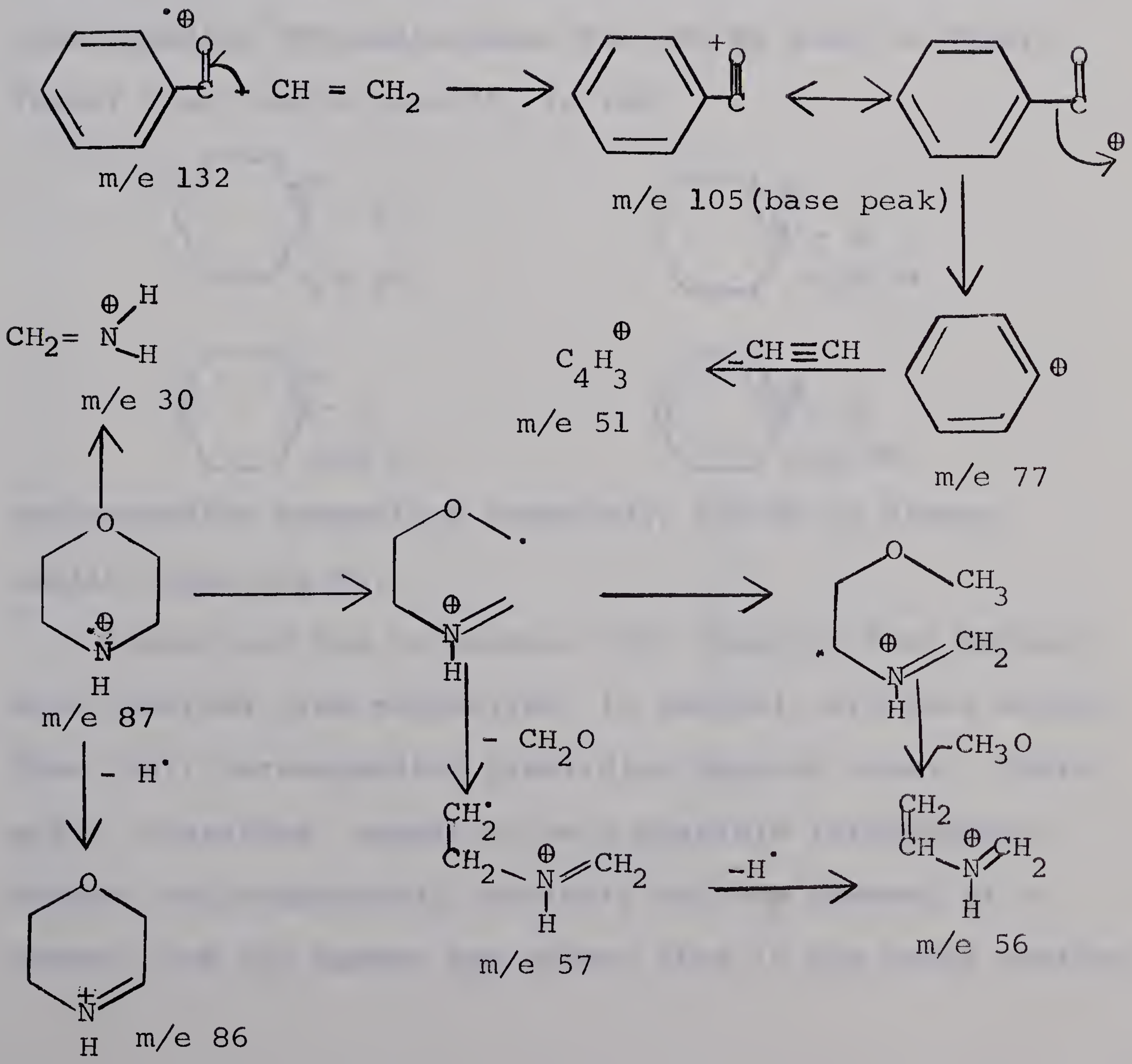


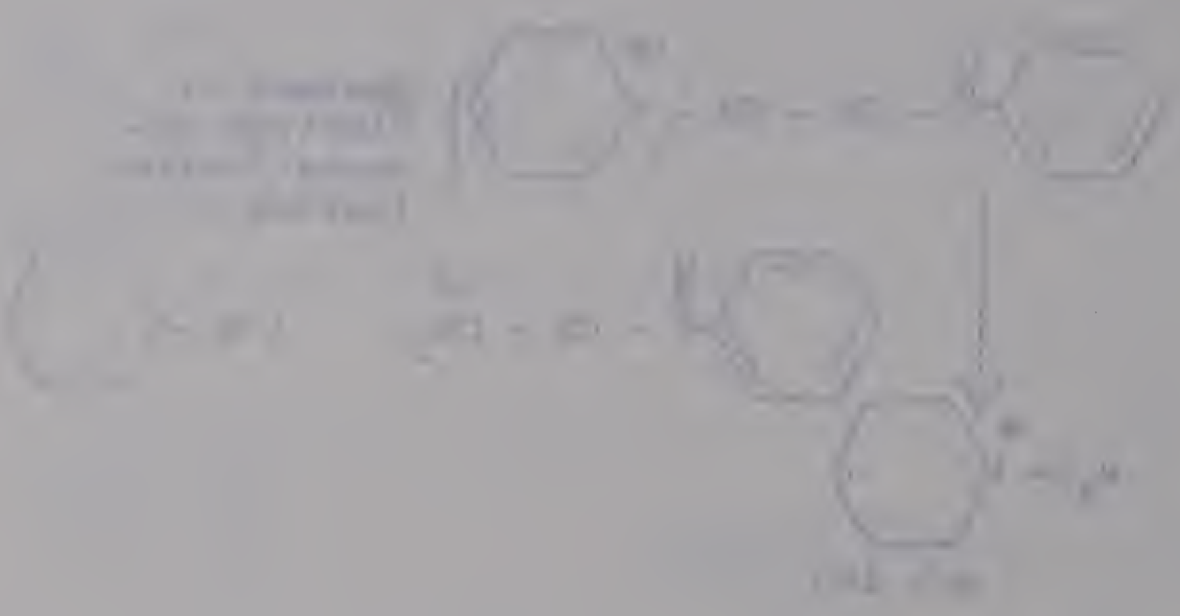


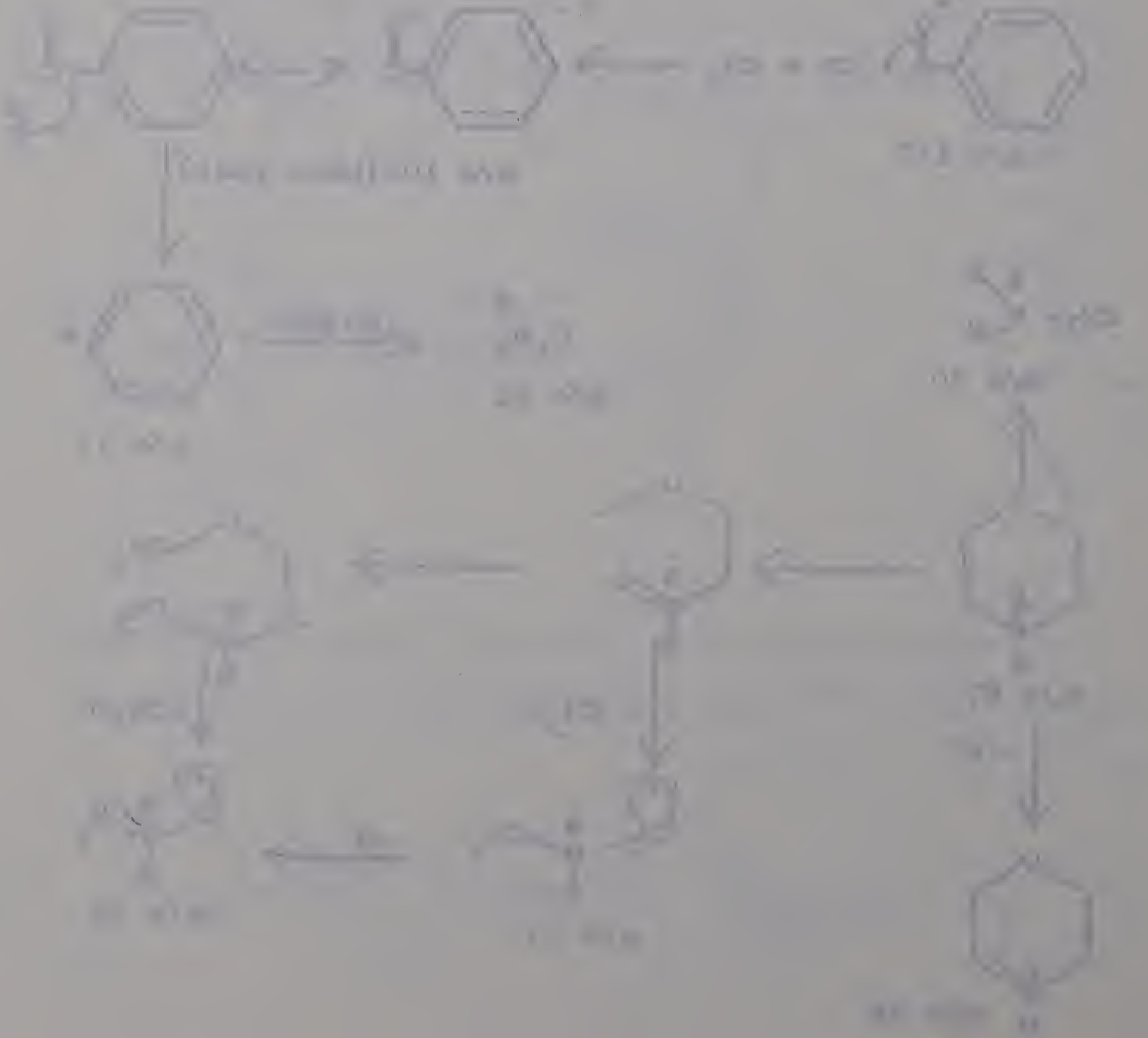
For the morpholinium compound, a similar fragmentation pattern results in peaks at m/e 132, 105, 100, 87, 86, 77, 57, 56, 55, 51, and 30.




C - CH - CH - N
Thermal or electron induced β-elimination
C - CH = CH2
+ H -N
H2C= N
m/e 100

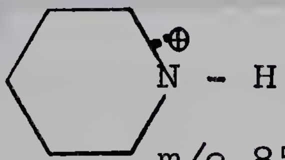

CH = CH2
m/e 132
m/e 105 (base peak)
CH≡CH
C4H3
m/e 51
m/e 77
CH2= N
m/e 30
m/e 87
- H•
m/e 86
- CH2O
CH2
CH2 - N = CH2
m/e 57
CH3
CH2
- CH3O
-H•
CH
m/e 56



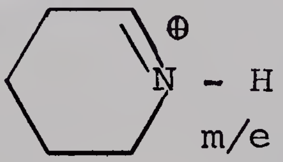


It is note-worthy that both β-piperidinoethyl phenyl ketone hydrochloride and β-morpholinoethyl phenyl ketone hydrochloride give a metastable ion at m/e 56.5. This shows that the peak at m/e 77 is obtained from the m/e 105 species in a single step. This would favour the mechanism suggested for this ion. In both these compounds the base peak was observed at m/e 105.

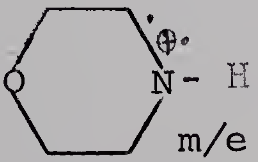
A very prominent and unexpected feature is observed in the mass spectra of Mannich bases where piperidine and morpholine compounds are used as the amine moieties (Fig. 1 and 2). Whereas, in piperidine Mannich bases and their corresponding hydrochlorides, the m/e 84 peak is always larger than that at m/e 85, in the corresponding morpholine compounds, m/e 86 is always smaller than m/e 87.



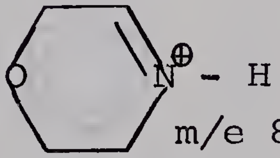
m/e 85



m/e 84



m/e 87



m/e 86

Denton and his co-workers (21) observed that Mannich bases derived from morpholine, in general, are less active than their corresponding piperidino Mannich bases. There might, therefore, appear to be a possible relationship between the antispasmodic activity and the removal of a proton from the number two carbon atom in the amine portion

FIGURE 1. Mass Spectrum of β-Piperidinoethyl Phenyl Ketone Hydrochloride.

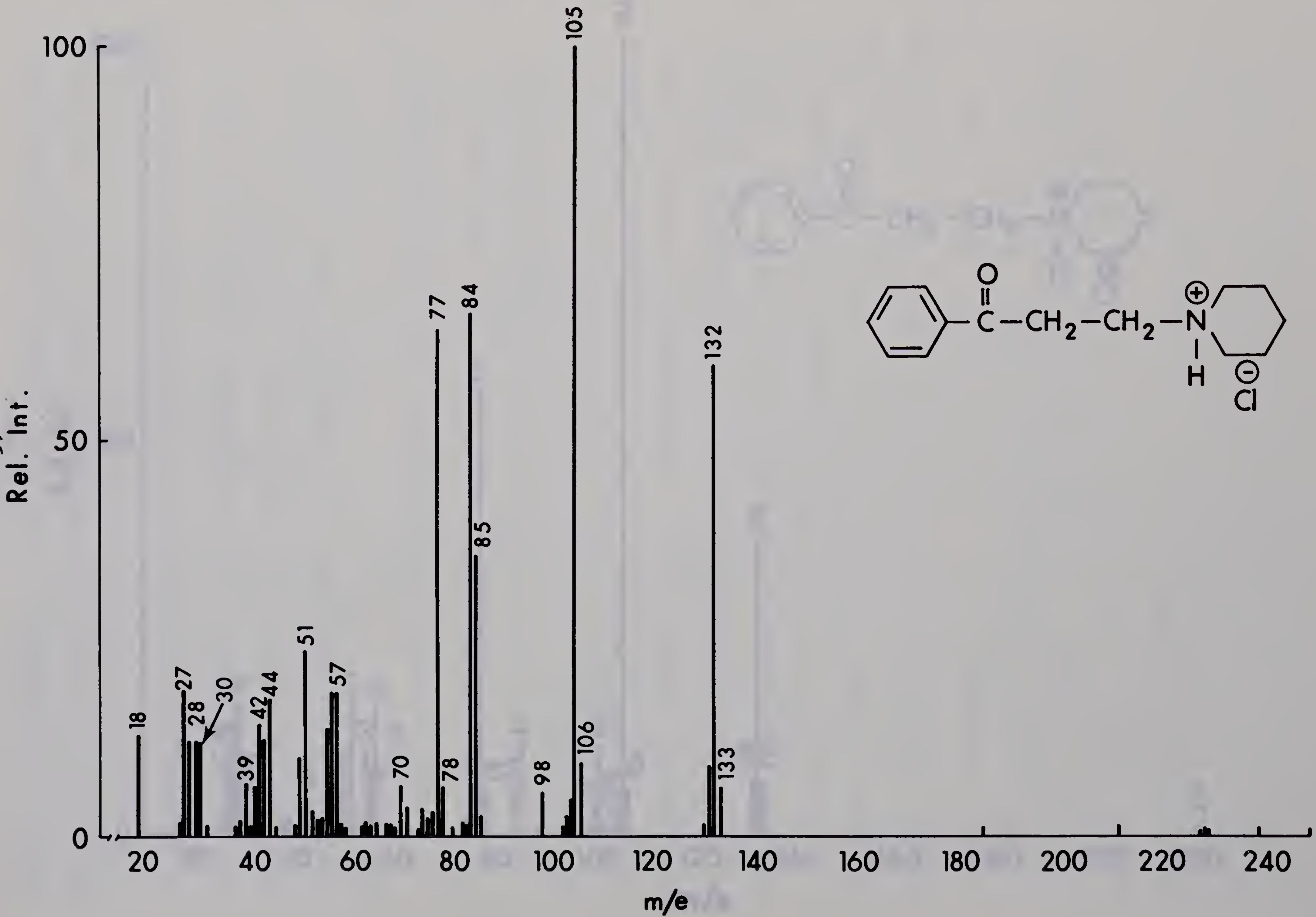
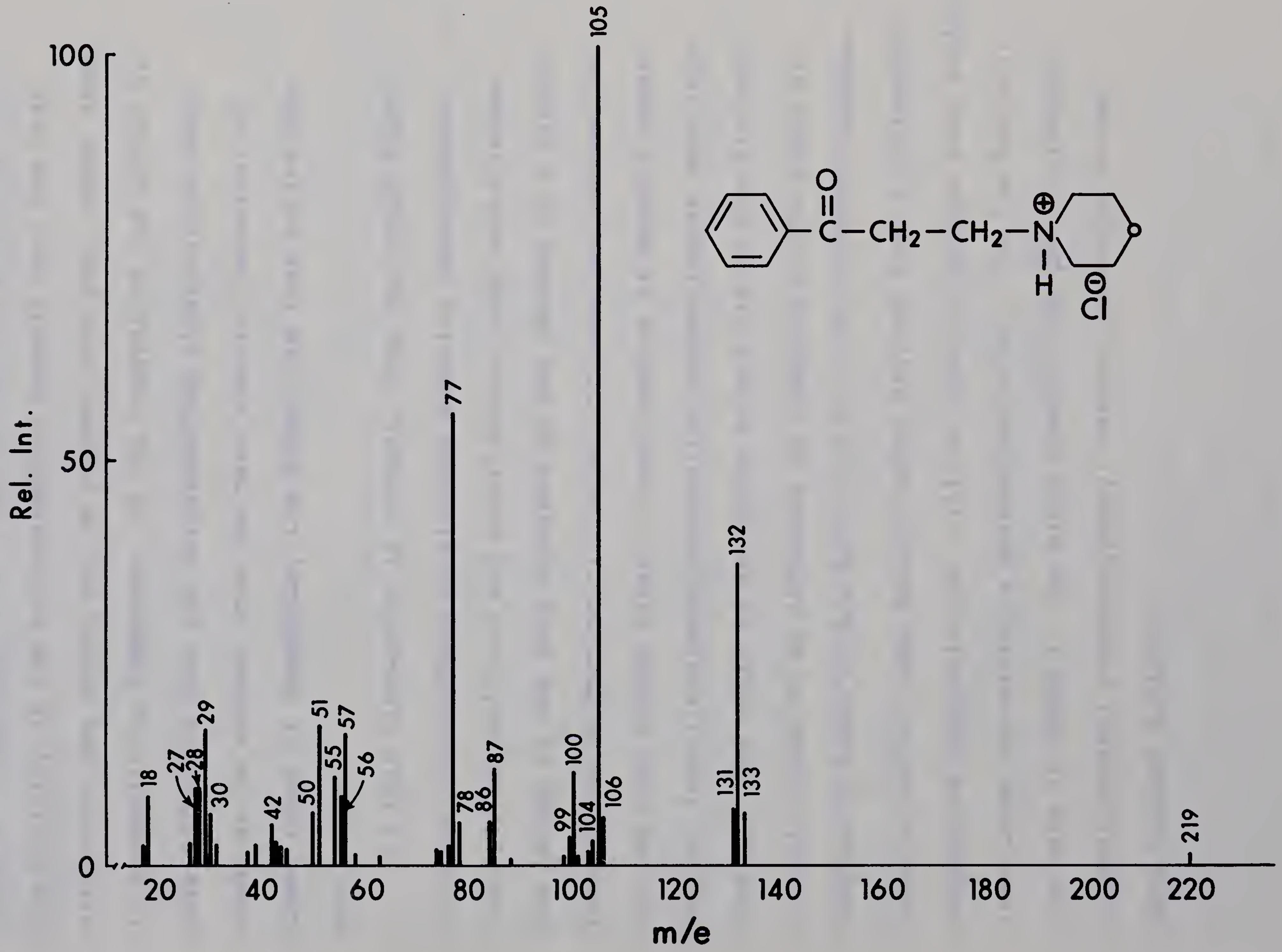


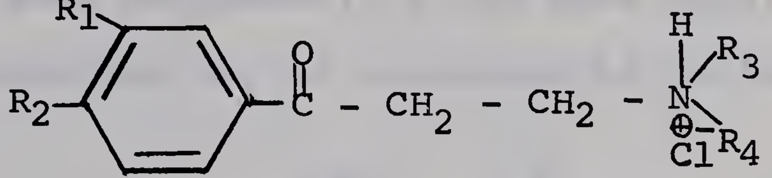
FIGURE 2. Mass Spectrum of β-Morpholinoethyl Phenyl Ketone Hydrochloride.



of the Mannich bases. One might suggest, therefore, that the activity of the antispasmodics depends upon the ease with which the proton may be removed from that carbon atom. In morpholinium compounds, as the removal of the proton is more difficult than the corresponding piperidinium compounds as is evident from the mass spectral behaviour of these types of compounds, the former are less active than the latter.

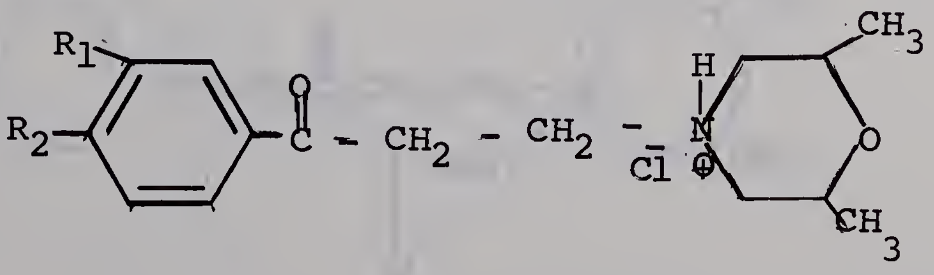
If this view-point is correct, then one would expect that the introduction of electron donating substituents into the morpholinium and piperidinium rings would reduce the length of the peak obtained by the removal of a proton from the amine portion of the Mannich bases as compared to the one with proton intact. Mass spectra of Mannich bases derived from 2,6-dimethylmorpholine hydrochloride were thus studied. The ratio of the peaks at m/e 114 to m/e 115 was actually found to be decreased as compared to the ratio of lengths of peaks at m/e 86 to m/e 87. If the above explanation is correct then Mannich bases derived from 2,6-dimethylmorpholine hydrochloride will be found to be even less active than those containing a morpholine moiety. On the basis of the data in Table 1, one might predict that β-2,6-dimethylmorpholinoethyl p-methoxyphenyl ketone hydrochloride may show unusual activity.

Table 1 - Comparison of Ratios of Some Peaks in Certain Mannich Bases:-



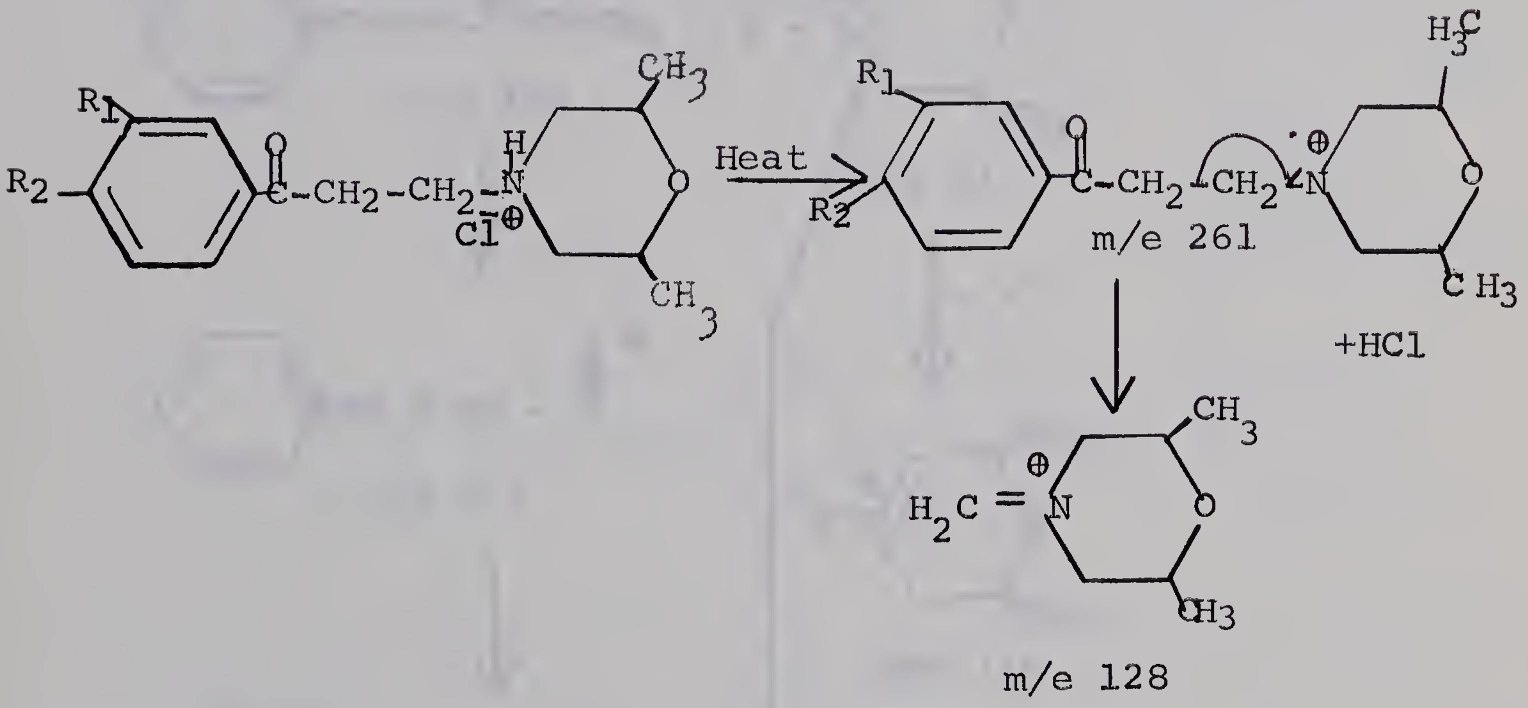
R_1	R_2	$-N\begin{smallmatrix}R_3\\R_4\end{smallmatrix}$ = Piperidine	$-N\begin{smallmatrix}R_3\\R_4\end{smallmatrix}$ = morpholine	$-N\begin{smallmatrix}R_3\\R_4\end{smallmatrix}$ =2,6-dimethyl-morpholine
		ratio of peaks 84/85	ratio of peaks 86/87	ratio of peaks 114/115
H	H	1.60	0.45	0.047
H	CH_3	1.80	0.30	0.30
H	OCH_3	2.0	0.30	1.30
NO_2	H	1.80	0.30	0.06
H	NO_2	1.80	0.30	0.025

It is interesting to note that in Mannich bases derived from 2,6-dimethylmorpholine hydrochloride having the general formula:-

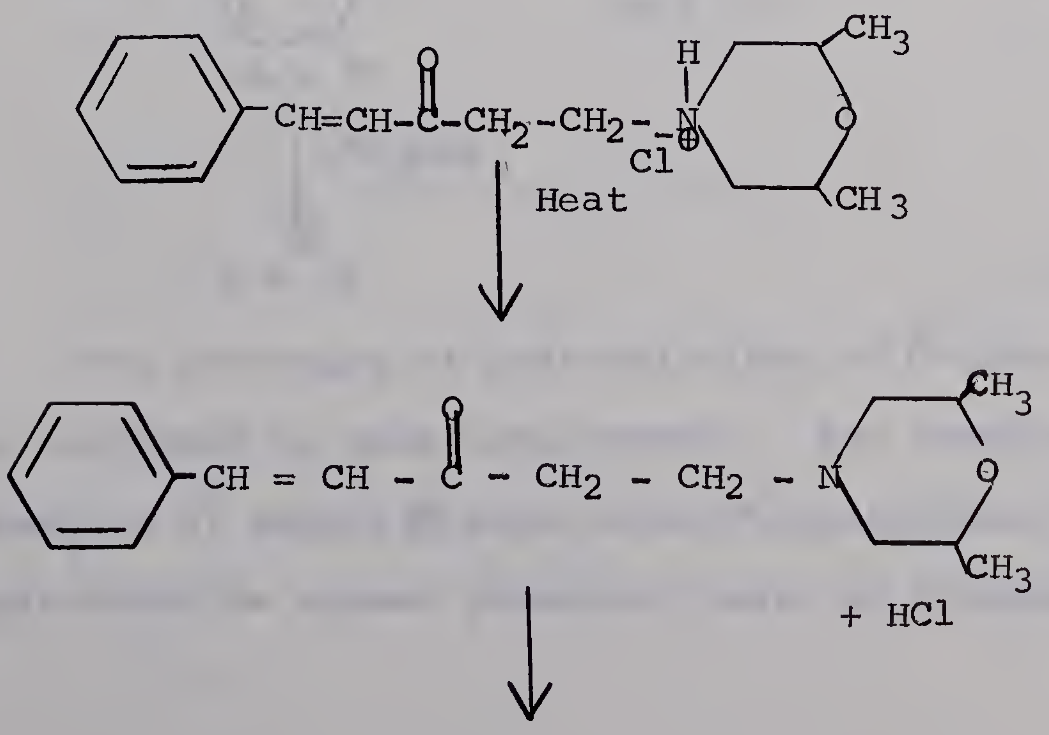


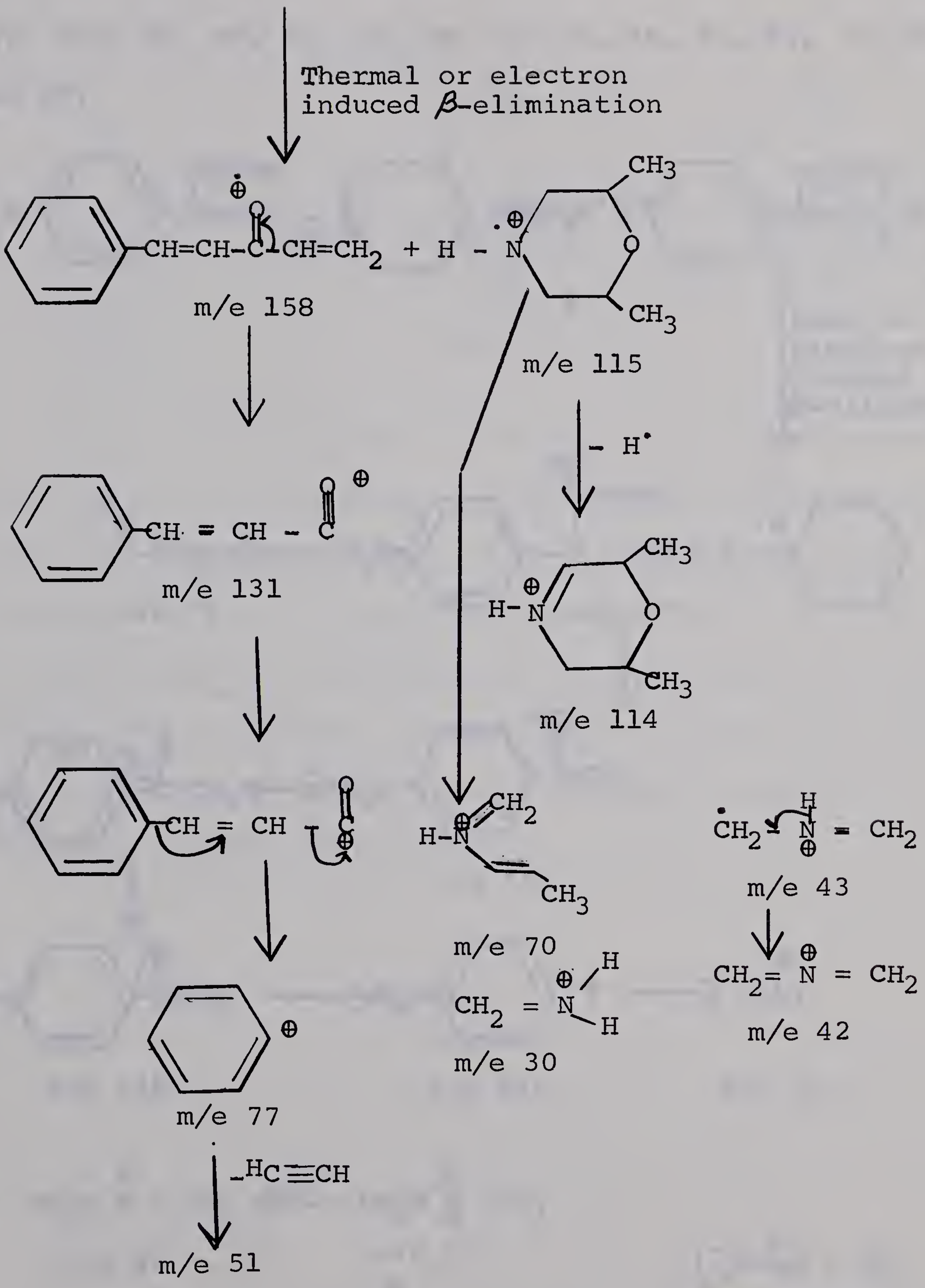
the mode of cleavage as suggested in the second plausible mechanism is not the major pattern. In most of the compounds except β-2,6-dimethylmorpholinoethyl phenyl ketone

hydrochloride and β-2,6-dimethylmorpholinoethyl-α-naphthyl ketone hydrochloride, a very sharp pleak appears at m/e 128 which, in some instances, is the base peak. The mechanism for its formation may be suggested as follows:-



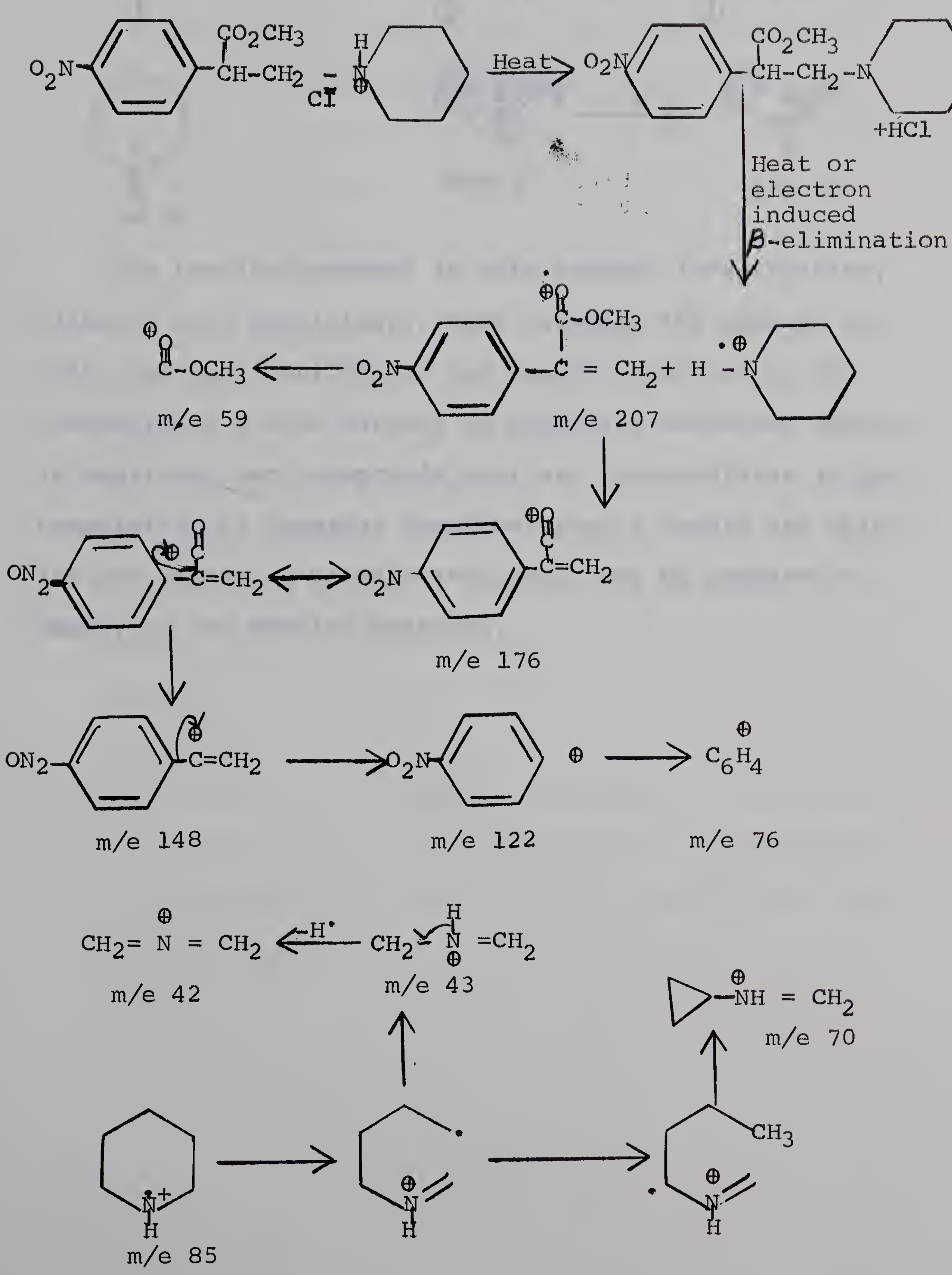
For β-2,6-dimethylmorpholinoethyl styryl ketone hydrochloride prominent peaks appear at m/e 158, 131, 115, 114, 77, 70, 51, 43, 42, and 30 which could be formed by the following mechanisms:-

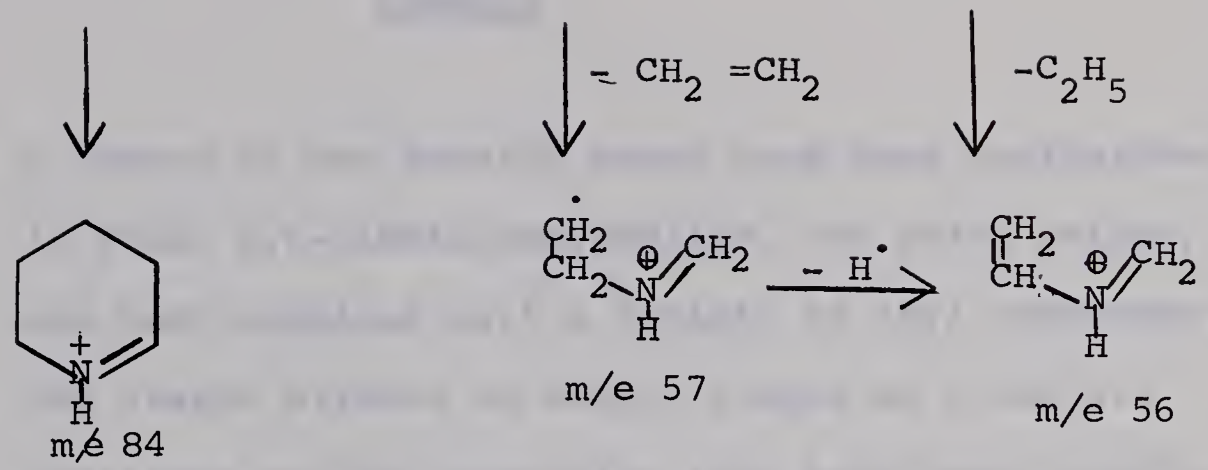




The structure of hydrochlorides of β-amino esters can be confirmed by mass spectrometry. For example, the mass spectrum of methyl β-piperidino-α-p-nitrophenylpropionate hydrochloride showed prominant peaks of interest at m/e 207,

176, 148, 85, 84, 76, 70, 59, 57, 56, 44, 43, 42, 30, 29 and 28.





The results reported in this present investigation, although only preliminary, have revealed the general utility and applicability of the Mannich reaction in the synthesis of a wide variety of potential medicinal agents. In addition, many compounds that are intermediates in the preparation of numerous chemotherapeutic agents and which are not otherwise readily available, may be prepared by employing the Mannich reaction.

SUMMARY

1. A number of new Mannich bases have been synthesized in which 2,6-dimethylmorpholine, the amine moiety, has been combined with a variety of acyl compounds.
2. The steric effects of methyl groups at 2 and 2,6 positions on the piperidine ring have been investigated.
3. In view of the utility of the Mannich bases derived from phenols, various amine moieties were combined with a number of phenolic compounds.
4. The relationship between mass spectra and the pharmacological activity of certain Mannich bases has been evaluated. A theory has been presented which may account for the superior antispasmodic activity of piperidino compounds as compared to those containing morpholine.
5. The utility of the Mannich reaction in the production of compounds which are intermediates in the synthesis of azasteroids and antidiarrhoeal compounds have been assessed.

EXPERIMENTAL

EXPERIMENTAL

All melting points were determined on a Thomas Hoover Capillary melting point apparatus which had been calibrated against melting point standards. Infrared spectra were recorded on a Perkin Elmer Infrared Spectrophotometer, Model 21. Mass spectra of the salts of the Mannich bases were obtained from an MS-9 mass spectrometer using direct probe introduction method. However, the mass spectra of free Mannich bases were determined on an MS-9 mass spectrometer using a heated inlet system, due to high volatility. Elemental analyses were performed by Dr.G. Weiler and F.B. Strauss, Microanalytical Laboratories, Oxford, England. All the yields reported were calculated on the basis of the amines used. All the chemicals were obtained from commercial sources and used without furthur purification unless otherwise specified.

GENERAL PROCEDURES

Method A.

A mixture of a ketone (0.10), a secondary amine hydrochloride (0.10 mole), paraformaldehyde (0.20 mole), and concentrated hydrochloric acid (0.50 ml.) in 50 ml. of absolute ethanol were heated under reflux. At the end of three hours another 0.10 mole of paraformaldehyde was added and refluxing continued for an additional six hours. Boiling acetone (200 ml.) was then added to the hot mixture with shaking. The resulting solution was allowed to stand at room temperature overnight and placed in the refrigerator for three hours. The crystalline product thus precipitated was separated by filteration. Ethanol and acetone proved to be a suitable solvent pair for crystallization.

Method B.

A mixture of a ketone (0.050 mole), paraformaldehyde (0.10 mole), a secondary amine hydrochloride (0.10 mole) and concentrated hydrochloric acid (0.50 mole) in 50 ml. of absolute ethanol was heated under reflux. At the end of three hours another portion of paraformaldehyde (0.05 mole) was added and refluxing

continued for an additional six hours. Boiling acetone (250 ml.) was then added to the hot mixture with shaking, and the resulting solution was allowed to stand at room temperature overnight and then placed in the refrigerator for three hours. No solid precipitated on cooling. The solvent was then removed on the evaporator and the residue recrystallized from acetone.

Method C.

p-Nitrophenylacetic acid (0.05 mole) in 25 ml. water was neutralized with a secondary amine (0.05 mole) and 37% formaldehyde solution (6 ml.) was added gradually with shaking. The resulting clear solution was heated at 40°C for twenty-four hours. A white solid began to separate after abour four hours. The crystalline product thus precipitated after twenty-four hours, was filtered. The residue was washed two times

continued for an additional six hours. Methanol [illegible] was then added to the hot mixture with cooling, and the resulting solution was allowed to stand at room temperature overnight and then placed in the refrigerator for three hours. No solid precipitated on cooling. The solvent was then removed on the evaporator and the residue crystallized from benzene.

Method 5.

p-Nitrophenylarsonic acid (0.05 mole) in 25 ml. water was neutralized with 4 N sodium hydroxide (0.05 mole) and 10% formaldehyde solution (8 ml.) was added gradually with stirring. The resulting clear solution was heated on a steam bath for [illegible] hours. A white solid formed [illegible] after about four hours. The crystalline [illegible] from [illegible] [illegible]. The [illegible] was washed two times

with absolute ethanol or preferably dry acetone in 50 ml. portion and dried.

Most of these acids turn red on standing, probably due to air oxidation.

Method D.

Thionyl chloride (20 ml.) was added to the β-amino acid (0.25 mole) drop-wise with cooling and shaking. After the completion of addition, the mixture was allowed to stand at room temperature for about 16 hours. During this period, the entire solid went into solution. The unreacted thionyl chloride was then removed on the evaporator. The residue was taken in carbon tetrachloride (100 ml.) 20 ml. of methanol was added drop-wise with shaking and the whole mixture was refluxed on steam-bath. After about 6 hours, the solvent and the unreacted methanol were removed on the evaporator and a portion of the resulting residue was recrystallized from acetone.

Method E.

Dry hydrogen chloride was passed through a solution of the secondary amine in acetone until precipitation was complete. The mixture was filtered and the residue recrystallized from ethanol and/or acetone.

COMPOUNDS PREPARED:-

Preparation of 2, 6-Dimethylmorpholine Hydrochloride (I):-

2, 6-Dimethylmorpholine hydrochloride was prepared by method E. The resulting solid was very hygroscopic and did not have a definite melting point.

Synthesis of β-2, 6-Dimethylmorpholinoethyl Phenyl Ketone Hydrochloride (II):-

β-2, 6-Dimethylmorphinoethyl phenyl ketone hydrochloride was synthesized in 72% yield using acetophenone, paraformaldehyde and 2, 6-dimethylmorpholine hydrochloride by method A. Melting point 195-196.5°C.

Anal. calcd. for $C_{15}H_{21}NO_2$ HCl: C, 63.48; H, 7.81; N, 4.93.
Found : C, 63.11; H, 7.69; N, 4.95.

Infrared spectrum:-

ν_{max}, 2670 - 2450 $(\overset{\oplus}{\mathrm{NH}})$, 1690 $(-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-)$, 1600-1580 (phenyl group) 1087 $(>\mathrm{CH{-}O{-}CH}<)$, 1460, 747 and 695 (monosubstituted benzene ring) cm^{-I}.

Mass-spectrum:-

m/e 247(0.2%), 132(42%), 128(2%), 115(19%), 114(0.9%), 105 (base peak) 77(62%), 71(24%), 56.5 (metastable peak), 56(11%), 55(10%), 51(21%), 42(19%), 39(5%), 38(1.5%), 36(0.3%), 30(48%).

Synthesis of β-2, 6-Dimethylmorpholinoethyl -4-Methyl Phenyl Ketone Hydrochloride (III):-

β-2, 6-Dimethylmorpholinoethyl -4-methyl phenyl ketone hydrochloride was prepared in 81% yield from p-methyl-

acetophenone, paraformaldehyde, and 2, 6-dimethylmorpholine hydrochloride using method A. Melting point 207-208^{o}C.

Anal, calcd. for $C_{16}H_{23}NO_2HCl$; C,64.53; H, 8.06; N, 4.70.
Found: C,64.52; H, 8.40; N, 4.37.

Infrared specturm (nujol-mull):-

νmax, 2680-2470 ($N\overset{+}{H}$), 1690($-\overset{\overset{O}{\|}}{C}-$), 1613-1580 (phenyl group), 1090(>CHO-CH<), and 860-800 (I, 4-disubstituted benzene ring) cm^{-I}.

Mass spectrum:-

m/e 261(15%), 146(12%), 128 (base peak), 119(58%), 115(7%), 114(2%), 98(6%), 84(6%), 71(12%), 70(8%), 65(10%), 56(67%), 42(28%), 41(15%), 38(29%), 30(22%).

Synthesis of β-2, 6-Dimethylmorpholinoethyl -4-Methyoxy-Phenyl Ketone Hydrochloride IV:-

β-2, 6-Dimethylmorpholinoethyl -4-methoxyphenyl ketone hydrochloride was synthesized in 60% yield from p-methoxyacetophenone, paraformaldehyde, and 2, 6-dimethylmorpholine hydrochloride using method A. Melting point 203-205^{o}C.

Anal. calcd. for $C_{16}H_{23}NO_2HCl$: C, 61.23; H, 7.70; N,4.46.
Found: C, 60.98; H, 7.70; N,4.39.

Infra-red spectrum (nujol-mull):-

νmax., 2680-2480 ($N\overset{+}{H}$), 1680($-\overset{\overset{O}{\|}}{C}-$), 1605-1578 (phenyl group), 1260 and 1225 (=C-O-C-), 1087 (>CH-OCH<), and 860-800 (I,4-disubstitutted benzene ring) cm^{-I}.

Mass-spectrum:-

m/e 277(13%), 163(7%), 162(8%), 135 (72%), 128 (base peak), 115(3%), 114(4%), 107(4%), 98(5%), 92(10%), 85(6%), 84(8%), 77(13%), 71(6%), 70(8%), 64(4%), 56(46%), 43(6%), 42(27%), 41(15%), 38(8%), 36(25%), 30(11%).

Synthesis of β-2, 6-Dimethylmorpholinoethyl -4-Biphenyl Ketone Hydrochloride V:-

β-2, 6-Dimethylmorpholinoethyl -4-biphenyl ketone hydrochloride was synthesized in 16% yield from biphenyl methyl ketone, paraformaldehyde, and 2,6-dimethylmorpholine hydrochloride using method A. Melting point 214-215°C.

Anal. calcd. for $C_{21}H_{25}NO_2HCl$:- C, 70.01; H, 7.23; N, 3.89.
Found: C, 70.07; H, 6.99; N. 3.82.

Infrared specturm (nujol-mull):-

νmax. 2700-2480 ($\overset{+}{NH}$), 1695 ($-\overset{O}{\overset{\|}{C}}-$), 1615, 1587 and 1515 (phenyl froup), 1090 ($\supset$CH -O- CH$\subset$), and 860-800 (I, 4-disubstituted benzene ring) cm^{-I}.

Synthesis of β-2, 6-Dimethylmorpholinoethyl -4-Chlorophenyl Ketone Hydrochloride VI:-

β-2, 6-Dimethylmorpholinoethyl-4-chlorophenyl ketone hydrochloride was synthesized in 63% yield from p-chloroacetophenone, paraformaldehyde and 2, 6-dimethylmorpholine hydrochloride using method A. Melting point 203.5-204.5°C.

Anal. calcd. for $C_{15}H_{21}NO_2HCl$:- C, 56.61; H, 6.65; N, 4.40.
Found: C, 56.47; H, 6.69; N, 4.33.

Infrared spectrum (nujol-mull):-

νmax., 2690-2490 ($\overset{+}{NH}$), 1695 ($-\overset{O}{\overset{\parallel}{C}}-$), 1595 and 1577 (phenyl group) 1095 ($>$CH-O-CH$<$) and 860-800 (I, 4-disubstituted benzene ring cm^{-I}.

Synthesis of β-2, 6-Dimethylmorpholinoethyl-3-Nitro Phenyl Ketone Hydrochloride VII:-

β-2, 6-Dimethylmorpholinoethyl-3nitro phenyl ketone hydrochloride was synthesized from m-nitroacetophenone, paraformaldehyde and 2, 6-dimethylmorpholine hydrochloride in 53% yield using method A. Melting point 196-197°C.

Anal. calcd. for $C_{15}H_{20}N_2O_4$ HCl:- C, 54.79; H, 6.40; N, 8.52.
Found: C, 54.55; H, 6.60; N, 8.58.

Infrared spectrum (nujol-mull):-

νmax., 2700-2350 ($\overset{+}{NH}$), 1700 ($-\overset{O}{\overset{\parallel}{C}}-$), 1615 and 1590 (phenyl group), 1540 and 1350 ($=$C-NO_2), 1093 ($>$CH-O-CH$<$), and 910-860 (one free H-atom on benzene ring) cm^{-I}.

Mass-spectrum:-

m/e 292 (8%), 177 (28%), 150 (80%), 128 (64%), 120 (7%), 115 (32%), 114 (2%), 104 (35%), 92 (8%), 77 (12%), 76 (32%), 71 (48%), 70 (16%), 56 (76%), 55 (75%), 50 (16%), 45 (16%), 43 (16%), 42 (52%), 41 (24%), 38 (15%), 30 (base peak), 28 (16%), 27 (36%).

Synthesis of β-2, 6-Dimethylmorpholinoisopropyl Phenyl Ketone Hydrochloride VIII:-

β-2, 6-Dimethylmorpholinoisopropyl phenyl ketone hydrochloride was synthesized in 68% yield from propiophenone, paraformaldehyde and 2, 6-dimethylmorpholine

hydrochloride by method A. Melting point 187-188.5°C.

Anal. calcd. for $C_{16}H_{23}NO_2$ HCl:- C, 64.65; H, 8.08; N,4.70
Found: C, 64.69; H, 8.24; N, 4.50.

Infrared-spectrum (nujol-mull):-

νmax., 2700-2500), (N$\overset{+}{H}$), 1680 (-$\overset{O}{\overset{\|}{C}}$-), 1600 and 1587 (phenyl group) 1087 (>CH-O-CH<), 1455, 765, and 704 (monosubstituted benzene ring) cm^{-I}.

Mass-spectrum:-

m/e 261(0.8%), 128 (base peak), 105(1.4%), 77(9%), 71(2%), 70(12%), 56(1%), 51(2%), 42(11%), 41(7%), 38(2%), 36(9%), 30(1%).

Synthesis of β-2, 6-Dimethylmorpholinoethyl -4-Nitrophenyl Ketone Hydrochloride IX:-

β-2, 6-Dimethylmorpholinoethyl -4-nitrophenyl ketone hydrochloride was synthesized in 61% yield from p-nitrophenyl-acetophenone, paraformaldehyde, and 2, 6-dimethylmorpholine hydrochloride using method A. Melting point 203-204°C.

Anal, calcd. for $C_{15}H_{20}N_2O_4$ HCl:- C, 54.79; H, 6.44; N, 8.52.
Found: C, 54.95; H, 6.02; N, 8.79.

Infrared-spectrum (nujol-mull):-

νmax., 2670-2450(N$\overset{+}{H}$), 1700(-$\overset{O}{\overset{\|}{C}}$-), 1610 (phenyl group), 1530 and 1350(=C-NO_2), 1087(>CH-O-CH<), 880-810 (I:4-disubstituted benzene ring) cm^{-I}.

Mass-spectrum:-

m/e 177(29%), 150(56%), 115(41%), 114(less than 1%),

104(20%), 76(13%), 71(50%), 59(13%), 58(17%), 56(21%), 55(33%), 42(39%), 38(2.4%), 36(0.001%), 30(base peak).

Synthesis of Benzalacetone X:-

The above ketone was obtained from benzaldehyde and acetone in the presence of sodium hydroxide according to the procedure of Organic Synthesis(67), in 73% yield; b.p.158° C/34mm. (Lit. reports(67) 120-130/7mm.).

Synthesis of β-2, 6-Dimethylmorpholinoethyl Styryl Ketone Hydrochloride XI:-

β-2, 6-Dimethylmorpholinoethyl styryl ketone hydrochloride was synthesized in 63% yield from benzalacetone, paraformaldehyde, and 2, 6-dimethylmorpholine hydrochloride using method A. Melting point 186-187°C.

Anal. calcd. for $C_{17}H_{23}NO_2$,HCl: C, 65.91; H, 7.75; N, 4.52.
Found: C, 65.61; H, 7.75; N, 5.04.

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2700-2480($\overset{+}{N}H$), 1665 and 1625 (α,βunsaturated ketone), 1575 (phenyl group), 1090($\rangle$CH-O-CH$\langle$), 748 and 688(monosubstituted benzine ring) cm^{-1}.

Mass-spectrum:-

m/e 195(0.9%), 159(6 %), 158(73%), 131(55%), 129(9%), 115(35%), 114(1%), 101(54%), 100(8%), 77(38%), 71(46%), 70(11%), 51(22%), 43(12%), 42(38%), 30(base peak).

Preparation of Piperazine Dihydrochloride XII:-

Piperazine dihydrochloride was prepared by method E. The resulting white solid melted at 335-336°C. (Lit. reports(92) 335-340°C.)

115(38%), 114(1.6%), 71(45%), 70(12%), 56(18%), 44(13%), 42(33%), 38(0.9%), 36(0.6%), 30(86%).

Synthesis of β2, 6-Dimethylmorpholinoethyl-2-Furyl Ketone Hydrochloride XV:-

β-2,6-Dimethylmorpholinoethyl-2-furyl ketone hydrochloride was synthesized in 7% yield from 2-acetylfuran, paraformaldehyde and 2, 6-dimethylmorpholine hydrochloride using method A.

Anal. calcd. for $C_{13}H_{19}NO_3$ HCl: C, 57.03; H, 7.31; N. 5.11.

Found - C, 55.20; H, 7.79; N, 4.90.

Anal. calcd. for $C_{13}H_{19}NO_3 HCl \frac{1}{2} H_2O$:C, 55.22; H, 7.43; N, 4.95.

Infrared-spectrum (nujol-mull):-

ν_{max},3550(OH bonded), 3080(=CH of furan), 1040-1015 (furan band), 880 (most characteristic peak of furans), 2670-2430($\overset{+}{NH}$), 1670($\overset{O}{\overset{\|}{C}}$), 1625-1015 (aro. furan ring).

Synthesis of β-2, 6-Dimethylmorpholinoethyl Methyl Ketone Hydrochloride XVI:-

β-2, 6-Dimethylmorpholinoethyl methyl ketone hydrochloride was synthesized in 42% yield from acetone (excess used), paraformaldehyde and 2, 6-dimethylmorpholine hydrochloride by method B. Melting point 156-157°C.

Anal. calcd. for $C_{10}H_{19}NO_2$ HCl: C, 54.17; H, 9.09; N, 6.32.

Found- C, 54.32; H, 9.09; N, 6.50.

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2670-2410 ($\overset{+}{NH}$), 1720($-\overset{O}{\overset{\|}{C}}-$), and 1087($\supset$CH-O-CH$\subset$)$cm^{-1}$.

Mass-spectrum:-

m/e 128(61%), 115(45%), 114(2.8%), 88.5(metastable peak),

71(56%), 70(52%), 56(base peak), 55(81%), 44(42%), 43(86%), 38(2%), 36(0.8%), 30(96%), 27(45%).

Preparation of 3-Methylpiperidine Hydrochloride XVII:-

3-Methylpiperidine hydrochloride was prepared by method E. The resulting white solid melted at 174-175.5°C.

Synthesis of β-3 Methylpiperidinoethyl Phenyl Ketone Hydrochloride XVIII:-

β-3-Methylpiperidinoethylphenyl ketone hydrochloride was synthesized in 81% yield from acetophenone, paraformaldehyde and 3-methylpiperidine hydrochloride using method A. Melting point 172-174°C.

Anal. calcd. for $C_{15}H_{21}NO.HCl$:- C, 67.29; H, 8.22; N, 5.23.

Found:- C, 67.29; H, 8.30; N, 5.15.

Infrared-spectrum:-

$\tilde{\nu}$max., 2670-2300($N\overset{+}{H}$), 1682$\left(-\overset{\overset{O}{\|}}{C}-\right)$, 1600 and 1580 (phenyl group), 773, 760 and 694 (monosubstituted benzene ring) cm^{-1}.

Preparation of 2,6-Dimethylpiperidine Hydrochloride XIX:-

2, 6-Dimethylpiperidine hydrochloride was prepared by method E. The melting point of the resulting white solid was 292°C.

Attempted Synthesis of 2, 6-Dimethylpiperidinoethyl Phenyl Ketone Hydrochloride XX:-

An attempt was made to synthesize 2,6-dimethylpiperidinoethyl phenyl ketone hydrochloride from acetophenone (12.0 g.), paraformaldehyde (6.0 g.), and 2,6-dimethylpiperidine hydrochloride, (10.0 g.). The resulting solid

(7.0 g.), melted at 293°C and melting point of a mixture of this material with authentic sample of 2, 6-dimethylpiperidine hydrochloride showed no depression indicating thereby that this material was unreacted 2,6-dimethylpiperidine hydrochloride.

The solvent was removed from the filtrate and the light yellow residue was distilled under reduced pressure to give 10.0 g. of a product, b.p. 98°/6mm.

Nuclear magnetic resonance spectrum of this material was as follows:

2-3.68τ (multiplet, 5.H); 7.50τ (singlet, 3.H), thus illustrating that this material b.p. 98°/6mm. was unreacted acetophenone.

Attempted Synthesis of 2,3,5-Tri(2, 6-Dimethylmorpholinomethyl)Hydroquinone XXI:-

In an attempt to synthesize 2,3,5-tri(2,6-dimethylmorpholinomethyl) hydroquinone, 2, 6-dimethylmorpholine (17.5 g, 0.15 mole) was added to hydroquinone (5.50 g, 0.05 mole) in 40 ml. water with vigorous shaking. Formaldehyde solution 37% (12.16 ml.) was added to the resulting clear solution. Heat was generated on the addition of formaldehyde solution. The resulting mixture was allowed to stand at room temperature. After about ½ hour, a liquid separated which soon solidified to a brown solid. The reaction was allowed to go to completion for about 12 hours. At the end of this time, the mixture was filtered. The residue was a sticky solid which weighed 16.60 g. Melting

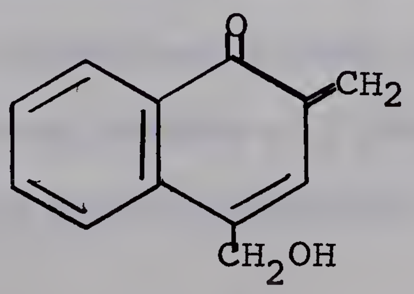
point was 170-220°C. A part of this sticky solid was recrystallized twice from anhydrous methanol to yield a white solid, melting point was 218-225°C. The analysis of this product showed that the resulting compound was di(2,6-dimethylmorpholinomethyl)-hydroquinone and not the expected 2,3,5-tri(2,6-dimethylmorpholinomethyl) hydroquinone.

Anal. calcd. for $C_{20}H_{32}N_2O_4$:- C, 65.99; H, 8.79; N, 7.69.

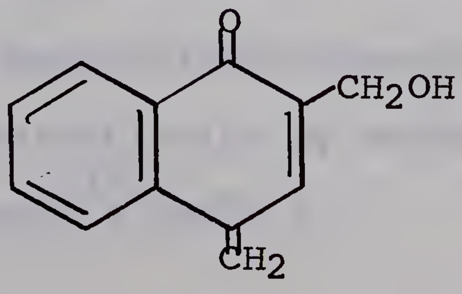
Found:- C, 65.92; H, 8.63; N, 7.39.

Attempted Synthesis of 2,6-Dimethylmorpholinomethyl-α-Naphthol Hydrochloride XXII:-

In an attempt to synthesize 2,6-dimethylmorpholinomethyl-α-naphthol hydrochloride from α-naphthol (7.20 g, 0.05 mole), paraformaldehyde (4.5 g, 0.15 mole) and 2,6-dimethylmorpholine hydrochloride (7.55 g, 0.05 mole) by method A.; a solid (4.41 g.) was obtained. Attempts to recrystallize this solid from an acetone-ethanol mixture and from ethanol alone were unsuccessful as the solid was insoluble in these solvents. This material melted at 301-304°C. The elemental analyses of this compound showed that the nitrogen was absent. On the basis of analyses and infrared spectrum, the following two structures were proposed:-



XXIV



XXIII

Anal. calcd. for $C_{12}H_{10}O_2$: C, 77.42; H, 5.38.

Found: C, 78.43; H, 5.45.

Preparation of Morpholine Hydrochloride XXV:-

Morpholine hydrochloride was prepared by method E. The resulting white solid melted at 177-178°C. (Lit. reports(93) 175-176°C.

Synthesis of β-Morpholinoethyl Phenyl Ketone Hydrochloride XXVI:-

β-Morpholinoethyl **phenyl** ketone hydrochloride was synthesized in 89% yield from acetophenone, paraformaldehyde and morpholine hydrochloride by method A. Melting point 186.5°C. (Lit. reports(30) 177°C.) (Aldrich Chemical Catalogue 186-187°C.)

Anal. calcd. for $C_{13}H_{17}NO_2HCl$: C, 61.06; H, 7.04; N, 5.47.

Found: C, 60.78; H, 6.93; N, 5.39.

Mass-spectrum:-

m/e 132(36%), 105(base peak), 87(11%), 86(5%). 77(54%), 57(16%), 56(8%), 55(9%), 51(16%), 38(0.2%), 36(0.1%), 30(6%).

Synthesis of β-Morpholinoethyl-4-Methylphenyl Ketone Hydrochloride XXVII:-

β-Morpholinoethyl-4-methylphenyl ketone hydrochloride was synthesized in 82% yield from p-methylacetophenone, paraformaldehyde and morpholine hydrochloride by method A. Melting point 224-225°C. (Lit. reports(21) 224°C.)

Infrared Spectrum (nujol-mull):-

$\nu_{max.}$, 2670-2350 ($\overset{+}{NH}$), 1680 ($-\overset{O}{\overset{\|}{C}}-$), 1612 and 1585 (phenyl group), 1150-1070 (ether linkage), and 860-800 (2 adjacent H atoms on benzene ring) cm^{-1}.

Mass-spectrum:-

m/e 146(45%), 119(base peak), 91(42%), 87(16%), 86(5%), 69.5 (metastable peak), 65(14%), 57(20%), 56(6%), 55(6%), 42(4%), 39(8%), 38(1%), 36(3%), 30(8%), 29(17%), 28(27%).

Synthesis of β-Morpholinoethyl-4-Methoxyphenyl Ketone Hydrochloride XXVIII:-

β-Morpholinoethyl -4-methoxyphenyl ketone hydrochloride was synthesized in 52% yield from para methoxyacetophenone, paraformaldehyde and morpholine hydrochloride using Method A. Melting point 209-210°C.

Anal. calcd. for $C_{14}H_{19}NO_3$ HCl: C, 58.83; H, 7.05; N, 4.90.
Found: C, 58.75; H, 7.05; N, 4.95.

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2620-2440 ($\overset{+}{NH}$), 1680($-\overset{O}{\overset{\|}{C}}-$), 1600 (phenyl group), 1260 and 1225(C-O-C), 1050-1010($=C-O-C$ sym. str.), 1150-1070($=C-O-C$ antisym. str.) and 860-800 (two H atoms on benzene ring) cm^{-1}.

Mass-spectrum:-

m/e 162(42%), 135(base peak), 107(6%), 92(11%), 87(16%), 86(5%), 77(16%), 64(5%), 63(5%), 57(21%), 56(5%), 55(6%), 42(4%), 38(2%), 36(0.1%), 30(8%), 29(18%), 27(8%),

Synthesis of β-Morpholinoethyl -3-Nitrophenyl Ketone Hydrochloride XXIX:-

β-Morpholinoethyl-3-nitrophenyl ketone hydrochloride was synthesized in 75% yield from meta nitroacetophenone, paraformaldehyde, and morpholine hydrochloride using method A. Melting point 186-187°C.

Anal. calcd. for $C_{13}H_{16}N_2O_4$ HCl: C, 52.00; H, 5.69; N, 9.31.
Found: C, 52.10; H, 5.67; N, 8.75.

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2670-2450 ($N\overset{+}{H}$), 1695 ($-\overset{O}{\overset{\|}{C}}-$), 1615 (phenyl group), 1535 and 1350 ($=C-NO_2$), 870, 803 and 780 (meta substituted benzene ring) cm^{-1}.

Mass-spectrum:-

m/e 177(29%), 150(base peak), 120(10%), 104(34%), 100(8%), 87(66%), 86(20%), 76(27%), 57(80%), 55(75%), 38(2%), 30(40%), 29(69%), 28(60%), 27(34%).

Synthesis of β-Morpholinoethyl-4-Nitrophenyl Ketone Hydrochloride XXX:-

β-Morpholinoethyl -4-nitrophenyl ketone hydrochloride was synthesized in 80% yield from p-nitroacetophenone, paraformaldehyde, and morpholine hydrochloride using method A. Melting point 206°C. (Lit. reports(94) 207-209°C.)

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2650-2440 ($N\overset{+}{H}$), 1695 ($-\overset{\overset{O}{\|}}{C}-$), 1600 (phenyl group), 1520 and 1345 ($=C-NO_2$), 1070-1150 (=C-O-C), 860-800 (1,4-disubstituted benzene ring) cm^{-I}.

Mass-spectrum:-

m/e 177(43%), 150(base peak), 120(28%), 104(37%), 92(17%), 87(64%), 86(20%), 76(25%), 55(83%), 54(22%), 53(61%), 43(11%), 42(16%), 38(3%), 36(0.7%), 30(34%), 29(76%), 28(45%), 27(34%).

Preparation of Piperidine Hydrochloride XXXI:-

Piperidine hydrochloride wa prepared by method E. The resulting white solid melted at 246-247°C. (Lit. reports(79) 246°C.)

Synthesis of β-Piperidinoethyl Phenyl Ketone Hydrochloride XXXII:-

β-Piperidinoethyl phenyl ketone hydrochloride was

synthesized in 84% yield from acetophenone, paraformaldehyde, and piperidine hydrochloride by method A. Melting point 191-192^{O}C.

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2640-2400($\overset{+}{NH}$), 1690(-$\overset{O}{\overset{\|}{C}}$-), 1600 and 1588 (phenyl group), 767, 757 and 694 (monosubstituted benzene ring) cm^{-I}.

Mass-spectrum:-

m/e 132(59%), 105(base peak), 98(4%), 85(35%), 84(65%) 77(65%), 70(6%), 57(17%), 56.5(metastable peak), 56(17%), 55(14%), 51(23%), 50(9%), 44(17%), 43(12%), 42(14%), 39(6%), 38(2%), 36(0.2%), 30(11%), 29(11%), 28(11%), 27(17%).

Synethesis of β-Piperidinoethyl -4-Methylphenyl Ketone Hydrochloride XXXIII:-

β-Piperidinoethyl -4-methylphenyl ketone hydrochloride was synthesized in 84% yield from p-methylacetophenone, paraformaldehyde, and piperidine hydrochloride using method A. Melting point 176.5^{O}C.

Infrared-spectrum(nujol-mull):-

$\nu_{max.}$, 2700-2350($\overset{+}{NH}$), 1685(-$\overset{O}{\overset{\|}{C}}$-), 1610 and 1575 (phenyl group), 860-830 (1,4-disubstituted benzene ring) cm^{-I}.

Mass-spectrum:-

m/e 146(41%), 119(base peak), 91(43%), 85(15%), 84(28%), 65(14%), 57(8%), 56(8%), 55(7%), 51(4%), 44(8%), 43(6%), 42(6%), 41(6%), 38(1%), 36(1%), 30(6%), 29(7%), 28(8%), 27(9%),

Synthesis of β-Piperidinoethyl -4-Methoxyphenyl Ketone Hydrochloride XXXIV:-

β-Piperidinoethyl -4-methoxyphenyl ketone hydrochloride was synthesized in 65% yield from p-methoxyacetophenone, paraformaldehyde, and piperidine hydrochloride using method A. Melting point 209-211°C. (Lit. reports(25) 216°C.)

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2670-2330$(\overset{+}{N}H)$, 1680 $(-\overset{O}{\overset{\|}{C}}-)$,1600(phenyl group), 1260 and 1230$(=C-O-C)$, 860-800(1, 4-disubstituted benzene ring)cm^{-1}.

Mass-spectrum:-

m/e 162(39%), 135(base peak), 113.5(metastable peak), 107(6%), 92(12%), 85(14%), 84(4%), 77(17%), 71(5%), 65(6%), 58(10%), 57(8%), 56.4(metastable peak), 56(15%), 45(7%), 44(14%), 43(6%), 38(0.7%), 36(0.1%), 32(12%), 30(9%), 29(9%), 28(14%),

Synthesis of β-Piperidinoethyl -3-Nitrophenyl Ketone Hydrochloride XXXV:-

β-Piperidinoethyl -3-nitrophenyl ketone hydrochloride was synthesized in 39% yield from m-nitroacetophenone, paraformaldehyde, and piperidine hydrochloride using method A. Melting point 178-179.5°C. (Lit. reports(26) 171-172°C.)

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2600-2350$(\overset{+}{N}H)$ 1696 $(-\overset{O}{\overset{\|}{C}}-)$, 1612 and 1580 (phenyl group), 1540 and 1350$(=C-NO_2)$, 875, 800 and 763(meta substituted benzene ring) cm^{-1}.

Mass-spectrum:-

m/e 177(29%), 150(base peak), 147(10%), 132(4%), 131(6%),

112(2%), 120(9%), 119(2%), 104(34%), 92(12%), 85(51%), 84(96%), 76(22%), 72(metastable peak), 70(10%) 65(5%), 57(27%), 5015%), 44(29%), 43(24%), 42(22%), 38(3%), 30(23%), 28(23%), 27(35%).

Synthesis of β-Piperidinoethyl -4-Nitrophenyl Ketone Hydrochloride XXXVI:-

β-Piperidionoethyl -4-nitrophenyl ketone hydrochloride wassynthesized in 70% yield from p-nitroacetophene, paraformaldehyde, and piperidine hydrochloride using method A. Melting point 193-195°C. (Lit. reports(94) 198-200°C.)

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2720-2500($N\overset{+}{H}$), 1700 ($-\overset{O}{C}-$), 1610 (phenyl group), 1520 and 1350($=C-NO_2$) and 860-800 (1,4-disubstituted benzene ring) cm^{-1}.

Mass-spectrum:-

m/e 177(8%), 150(27%), 146(7%), 120(19%), 104(7%), 98(3%), 92(6%), 85(53%), 84(base peak), 76(5%), 70(9%), 65(4%), 57(30%), 56(30%), 55(12%), 50(4%), 44(30%), 43(23%), 42(23%), 41(10%), 39(8%), 38(1%), 30(26%), 29(26%), 28(26%).

Synthesis of β-Piperidino-α-p-Nitrophenylpropionic Acid XXXVII:-

β-Piperidino -α- p-nitrophenylpropionic acid was synthesized in 58% yield from p-nitrophenylacetic acid paraformaldehyde solution 37% and piperidine using method C. Melting point 136°C. (Lit. reports(74) 138°C.)

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2500-2000($N\overset{+}{H}$), 1630($\overset{-}{CO_2}$), 1515 and 1330 ($=C-NO_2$) and 860 and 840(1,4-disubstituted benzene ring) cm^{-1}.

Synthesis of Methyl β-Piperidino-α-p-Nitrophenylpropionate Hydrochloride XXXVIII:-

Methyl β-piperidino-α-p-nitrophenylpropionate hydrochloride was synthesized in quantitative yield from XXXVII by esterification using method D. Melting point 211°C.

Anal. calcd. for $C_{15}H20\ N_2O_4.HCl$: C,54.79; H, 6.44; N,8.52.
Found: C,54.68; H, 7.21; N,8.44.

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2570-2470($\overset{+}{N}H$), 1730($-\overset{\overset{O}{\|}}{C}-$), 1600 (phenyl group), 1530 and 1345($=C-NO_2$), 862-840(1,4-disubstituted benzene ring) cm^{-1}.

Mass-spectrum:-

m/e 207(91%), 176(18%), 148(46%), 118(20%), 102(22%), 90(12%), 85(54%), 84 (base peak), 76(10%), 70(8%), 59(11%), 57(32%), 56(28%), 55(10%), 44(26%), 43(24%), 42(21%), 39(11%), 38(2%), 36(0.5%), 30(23%), 29(27%), 28(24%).

Synthesis of β-2, 6-Dimethylmorpholino-α-p-Nitrophenylpropionic Acid,XXXIX,:-

β-2, 6-Dimethylmorpholino-α-p-nitrophenylpropionic acid was synthesized in 88% yield from p-nitrophenyl acetic acid, formaldehyde solution(37%), and 2,6-dimethylmorpholine using method D. Melting point 142-143°C.

Infrared-spectrum:-

$\nu_{max.}$, 2500-1800 broad ($\overset{+}{N}H$), 1640($\overset{-}{CO_2}$), 1605 (phenyl group), 1520 and 1340 ($\equiv C-NO_2$), 1095 ($>CH-O-CH<$), and 850-840 (1,4-disubstituted benzene ring)cm^{-1}.

Synthesis of Methyl β-2,6-Dimethylmorpholino- α-p-Nitrophenylpropionate Hydrochloride XL:-

Methyl β-2,6-dimethylmorpholino- α-p-nitrophenylpropionate hydrochloride was synthesized in 68% yield from XXXIX using method D. Melting point 150-152°C.

Anal. calcd. for $C_{16}H_{22}N_2O_5.HCl$: C, 53.56; H, 6.46; N, 7.80.
FoundL C, 53.73; H, 6.67; N, 7.62.

Infrared-spectrum (nujol-mull):-

νmax., 2900 (-CH stretching), 2530-2220 broad ($\overset{+}{NH}$), 1737 ($-\overset{O}{\overset{\|}{C}}-$), 1600 (phenyl group), 1530 and 1343 ($=C-NO_2$), 1082 ($>CHO-CH<$), and 860-830 (1,4-disubstituted benzene ring) cm^{-1}.

Mass-spectrum:-

m/e 207 (0.7%), 177 (0.4%), 148 (0.6%), 128 (base peak), 119 (0.7%), 118 (0.6%), 115 (0.5%), 114 (0.2%), 103 (0.9%), 102 (0.7%), 77 (1%), 71 (2%), 70 (4%), 42 (16%), 41 (5%), 38 (33%), 36 (6%).

Attempted Synthesis of β-2,6-Dimethylpiperidino- α-p-Nitrophenylpropionic Acid XLI:-

β-2.6-Dimethylpiperidino- α-p-nitrophenylpropionic acid synthesis was attempted from p-nitrophenylacetic acid, formaldehyde solution (37%) and 2,6-dimethylpiperidine using method C. No solid separated on heating the contents at 40°C for 24 hours.

Attempted Synthesis of β-2-Methylpiperidino-α-p-Nitrophenylpropionic Acid. XLII:-

β-2-Methylpiperidino - α-p-nitrophenylpropionic acid was attempted from p-nitrophenylacetic acid, formaldehyde

solution (37%), and 2-methylpiperidine using method C. No solid separated on heating the contents at 40°C for 24 hours.

Synthesis of β-Dimethyamino-α-p-Nitrophenylpropionic Acid XLIII:-

β-Dimethylamino-α-p-nitrophenylpropionic acid was synthesized in 65% yield from p-nitrophenylacetic acid, formaldehyde solution (37%), and dimethylamine using method C. Melting point 159°C.

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2500–2200 ($\overset{+}{N}H$), 1640 ($C\bar{O}_2$), 1610 and 1600 (phenyl group) 1515 and 1335 ($=C-NO_2$), and 870–820 (1,4-disubstituted benzene ring) cm^{-I}.

Synthesis of Methyl β-Dimethylamino-α-p-Nitrophenylpropionate Hydrochloride XLIV:-

Methyl β-dimethylamino-α-p-nitrophenylpropionate hydrochloride was synthesized in 79% yield from XLIII using method D. Melting point 166–167°C.

Anal. calcd. for $C_{12}H_{16}N_2O_4.HCl$: C, 49.91; H, 5.89; N, 9.70.
Found: C, 49.82; H, 5.72; N, 10.71.

Infrared-spectrum (nujol-mull):-

$\nu_{max.}$, 2650–2220 ($\overset{+}{N}H$), 1742 ($-\overset{O}{\overset{\|}{C}}-$), 1612 and 1600 (phenyl group). 1537 and 1350 ($=C-NO_2$), 1167 ($R-\overset{O}{\overset{\|}{C}}-\underline{O-CH_3}$), and 852 (1,4-disubstituted benzene ring) cm^{-I}.

Synthesis of β-Methylamino-α-p-Nitrophenylpropionic Acid XLV:-

β-Methylamino-α-p-nitrophenylpropionic acid was synthesized in 36% yield from p-nitrophenylacetic acid, and formalde-

hyde solution (37%) and methylamine using method C. Melting point 162.5°C.

Anal. calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.36; N, 12.50.

Found: C, 53.18; H, 5.43; N, 12.25.

Infrared-spectrum (nujol-mull):-

max., 2700-2250($\overset{+}{NH}$), 1665($\overset{-}{CO_2}$), 1600 (phenyl group) 1515 and 1350($=$C-NO_2), 865-815(1,4-disubstituted benzene ring)cm^{-I}.

Preparation of β-Piperidinoethyl Phenyl Ketone XLVI:-

β-Piperidinoethyl phenyl ketone hydrochloride XXXII (6.0g.) was taken in water (50 ml.) and basified with 15% sodium hydroxide. The aqueous portion so obtained was extracted with three 50 ml. portions of chloroform. The combined chloroform layers were dried over anhydrous potassium-carbonate and filtered. The solvent was removed from the filtrate and the resulting residue (a colourless oil) on drying weighed 4.90 g. Yield was 100%.

Mass-spectrum:-

m/e 132(45%), 120(3%), 105 (base peak), 98(6%), 85(28%), 84((53%), 77(71%), 57(19%), 56(20%), 55(15%), 51(28%), 50(10%), 44(17%), 43(13%), 42(14%), 39(7%), 38(2%), 36(0.2%), 30(17%), 29(17%), 28(17%).

Preparation of β-Piperidinoethylphenyl Ketone Methiodide XLVII:-

β-Piperidinoethylphenyl ketone (1.72 g.) was refluxed with methyl iodide (5 ml.) in methanol (30 ml.) for four hours. The solvent and the unreacted methyl iodide were

removed on the evaporator. The residue was a light yellow solid which on recrystallisation from methanol gave a white solid (1.115). This material melted at 194-198°C.

Infrared-spectrum:-

ν_{max}, 2700 and 2500 ($\overset{+}{N}$-CH$_3$), 1680 (-$\overset{O}{\overset{\|}{C}}$-), 1600 and 1580 (phenyl group), 747 and 690 (monosubstituted benzene ring) cm^{-1}.

Mass-spectrum:-

m/e 142(0.8%), 132(36%), 120(7%), 105 (base peak), 98(5%), 99(2%), 85(2%), 84(4%), 77(66%), 70(1%), 57(2%), 56(2%), 55(10%), 51(26%), 50(9%), 43(4%), 42(3%), 39(3%), 39(1%), 27(10%),

Preparation of β-2,6-Dimethylmorpholinoethyl Phenyl Ketone XLVIII:-

β-2,6-dimethylmorpholinoethyl phenyl ketone hydrochloride(6.0 g.) was taken up in water (50 ml.), and basified with 15% sodium hydroxide. The aqueous portion so obtained was extracted with three 50 ml. portions of chloroform. The combined chloroform layers were dried over anhydrous potassium carbonate, and filtered. The solvent was removed from the filtrate and the resulting residue (a colourless oil) on drying gave a white solid in quantitative yield.

Mass-spectrum:-

m/e 247(0.9%), 132(45%), 128(9%), 115(24%), 114(1%), 105 (base peak), 77(69%), 71(38%), 56.5 (metastable peak), 56(24%), 55(13%), 51(28%), 50(10%), 42(34%), 41(13%), 29(8%), 38(2%), 36(0.4%), 30(82%).

Preparation of β-2,6-Dimethylmorpholinoethyl Phenyl Ketone Methiodide XLIX:-

β-2,6-Dimethylmorpholinoethyl phenyl ketone XLVIII, (2.25 g.) was refluxed with methyliodide (5 ml.) in methanol (30 ml.) for 4 hours. The solvent and the unreacted methyliodide were removed on the evaporator. The residue weighed 3.50 g. and melted at 190-191°C.

Infrared-spectrum (nujol-mull):-

νmax., 2700 and 2600($\overset{+}{N}$-CH_3), 1680 ($-\overset{O}{\overset{\|}{C}}-$), 1600 and 1580 (phenyl group), 1087(>CH-O-CH<), 747 and 687 (monosubsubstituted benzene ring) cm^{-1}.

Mass-spectrum):-

m/e 142(3%), 132(35%), 129(3%), 128(0.3%), 120(8%), 115(16%) 105 (base peak), 77(69%), 71(24%), 70(6%), 56.5(metastable peak), 56(12%), 55(10%), 51(26%), 50(10%), 43(21%), 42(26%) 41(9%), 39(7%), 38(2%), 30(54%).

Synthesis of p-Chlorophenylacetic Acid L:-

p-Chlorophenylacetonitrile (19.56 g.) was added to concentrated hydrochloric acid (100 ml.) gradually with cooling and shaking. The entire mixture was allowed to stand at room temperature for about 12 hours. Hydrogen chloride was then passed through it for 5 minutes and the mixture was heated on a steam bath for 5 hours. It was then cooled to room temperature and refrigerated for 3 hours. The precipitated solid (15.06 g.) which melted at 101-103°C. was separated by filtration (Lit. reports(93)

m.p. 105-106°C. and 100°C).

Attempted Synthesis of β-Piperidino-α-p-Chlorophenylpropionic Acid LI:-

The synthesis of β-piperidino-α-p-chlorophenylacetic acid was attempted using chlorophenylacetic acid, formaldehyde solution (37%) and piperidine using method C. No solid separated on heating the contents at 40°C. for 24 hours.

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